**Contributions:**
- Syntheses of Catechol Diterpenes and Their Biological Activities
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**New Products Information:**
- Useful Organocatalyst for Acid-free Acetalization
- 1,8-Diaminonaphthalene-masked Boronic Acids
- Stable Fluorinating Reagent with Ease of Handling “FLUOLEAD™”
- Useful N-Heterocyclic Carbene Precatalysts “Bode Catalysts”
- Reduction of Alcohols
- Strong Organic Bases
- A Useful Brominating Reagent
- A Useful Condensation Activator Bearing Less Nucleophilicity and No Deliquescence
- Selective Fluorination of Hydroxy Group Using DFMA
- Electrophilic Iodinating Reagent
- Air-stable Tri-tert-butylphosphine Equivalent
- Reagent of the Preparation for Amine-Reactive Water-Soluble Labels
1. Biological activities of catechol diterpenes

A bioactive organic compound has a unique three-dimensional structure with specific functional groups in required positions on the skeleton. In general, derivatives of the same skeleton without the functional groups show very low or no biological activity. Synthesis of a bioactive compound requires easy introduction of the functional groups into the skeleton. Successful synthesis of a bioactive compound with a complex structure may result in the discovery of novel organic reactions, but may provide only a few mg of the desired compound. However, investigation on the biological activities of a compound requires a large amount of the compound. Development of a facile synthesis of an important bioactive compound in large quantities may produce new science.

Recently, many studies on the bioactivity of anti-oxidants in food have been reported. Anti-oxidants in foods include vitamins, sulfur compounds, and many polyphenols. Because the polyphenols can be oxidized by oxygen, they are unstable in air. Natural polyphenols can be classified as flavonoids (e.g., catechins in teas), stilbenes (e.g., resveratrol in wines), phenolic diterpenes (anti-oxidants in rosemary), phloroglucinols (anti-oxidants in hops) and so on. Many anti-oxidants also show other various bioactivities, such as plant defense compounds against fungi, bacteria, or insects.1-10

2. Ortho-quinone and ortho-quinone methide

Among the polyphenols, catechols are easily oxidized to ortho-quinones, which are tautomeric isomers of 2-hydroxy-1,4-

Fig. 1. Tautomeric isomerizations between cyclopenta-1,2-dione and 2-hydroxy-2-cyclopentenone, and between ortho-quinone and ortho-quinone methide.

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Fig. 2. Diterpenes with the quinone methide structure.
quinone methide (ortho-quinone methide). As both tautomeric isomers are unstable, few reports on the chemical reactivity and bioactivity of ortho-quinone methides exist.

No study on the equilibrium bias between ortho-quinone and ortho-quinone methide has been reported. The tautomeric equilibrium between ortho-quinone and ortho-quinone methide is similar to the tautomeric equilibrium between cyclopenta-1,2-dione and 2-hydroxy-2-cyclopentenone. In the equilibrium, 2-hydroxy-2-cyclopentenone exists as the only isomer (Fig. 1).

The MOPAC calculation of abietaqueinone methide (1), a natural diterpene, showed that the major isomer is ortho-quinone methide, which is in agreement with our experiment.6,11) Many stable natural ortho-quinone methide diterpenes have been reported, e.g., abietaqueinone methide11) (1) (possesses anti-MRSA and anti-VRE activity, and is used as a remedy for intestinal worms in east Africa), taxodione12-14) (2) and taxodone12-14) (3) (possess anticancer activity), 3-O-benzylophloxozone10) (4) (possesses antimalarial activity), maytenoquinone13,16-18) (5) and sageaqueinone methide13) (6) (possess anti-viral activity) (Fig. 2). Therefore, we investigated the synthesis and the bioactivities of diterpenes with quinone methide and related compounds.

3. Total syntheses of diterpenes with an abietane skeleton via the stereo-selective cyclization of polyenes

Diterpenes with an abietane skeleton are biologically synthesized via sequential cyclizations of geranylgeranylphosphates. For our total synthesis of abietane diterpenes, the stereo-selective cyclization of a modified polyene ester (7) was examined.19)

The modified polyene 7 produced an asymmetric center at C7 in the cyclized products (8 and 9). Stereochemistry of the products was changed due to the alkyl group of the ester at C7 during the cyclization of 7 with Lewis acid BF₃·OEt₂ in nitromethane (Fig. 3). Larger alkyl esters such as isopropyl or menthyl produced more stereoselectivity compared to the methyl ester (Fig. 3). This selectivity can be explained by the difference in stability between two transition states (I and II) to give 8 and 9, respectively. Transition state I may have greater steric repulsion between the ester group and the aromatic hydrogen, compared to transition state II. Therefore, the larger alkyl ester 7 afforded 9 selectively through the more stable transition state II during cyclization.

This stereo-selective cyclization of modified polyenes was applied to the total syntheses of 12 diterpenes. The synthesis of racemic ferruginol20,21) (16) from the cyclized product 9 is
shown in Fig. 4. The ester group of 9 was hydrolyzed to give the carboxylic acid 10, which was then heated with Pb(OAc)₄-Cu(OAc)₂ in pyridine to form the 6,7-unsaturated compound 11. Compound 11 was hydrogenated to give tricyclic methyl ether 12. The isopropyl group was introduced on the aromatic ring in three steps, Friedel-Crafts acylation, Wittig reaction, and hydrogenation, to give ferruginol methyl ether (15). Methyl ether 15 was treated with ethanethiol and sodium hydride in N,N-dimethylformamide (DMF) at 120 °C for 2 days to give (+)-ferruginol (16). (+)-Ferruginol (22) was synthesized from the acid 17, which was treated with (S)-BINOL, DCC, and DMAP to give (S)-BINOL ester 18. The chiral ester was treated with LDA, HMPA, and geranyl chloride (19) in 95% de. The (S)-BINOL ester 20 was treated with BF₃·OEt₂ in nitromethane to afford cyclized BINOL ester 21 stereoselectively. The ester 21 was converted to (+)-ferruginol 22 by procedures similar to those for racemic ferruginol (16) (Fig. 5). (−)-Ferruginol (23) was synthesized using (R)-BINOL via similar reactions.

4. Synthesis of (±)-totarol

The totarane skeleton has an isopropyl group at C14, whereas abietane has an isopropyl group at C13. A typical totarane compound, totarol 22(29), was synthesized as a racemate from another modified polyene 28 (Fig. 6). 2-Methoxy-6-methylbenzoic acid (24) was methylated with CH₃I and K₂CO₃ in CH₃CN to afford sugiol (25), whose methyl ether was deprotected with EtSH and NaH in DMF to afford sugiol (34). Introduction of a double bond

5. Syntheses of highly oxidized diterpenes with an abietane skeleton and their anti-MRSA and anti-VRE activities

The oxidized abietane diterpenes, abietaquione methide (1), taxodione (2), 6,7-dehydroferruginol methyl ether (11), ferruginol (15), royleanone (30) via ortho-oxidation at C14), demethyleriptopojaponol (31) and salvinolone (32) via oxidation at the C7, benzylic position) using protecting groups. In the route B, dehydroferruginol methyl ether (11) was oxidized by hydroboration and Jones’ oxidation to give sugiol methyl ether (33), whose methyl ether was deprotected with EtSH and NaH in DMF to afford sugiol (34).
at C5-6 of 11 produced 5,6-dehydrosugiol methyl ether (35) and 5,6-dehydrosugiol (36). In the route C, dehydroferruginol methyl ether (11) was oxidized with m-chloroperbenzoic acid (mCPBA) and then treated with TsOH to give 6-oxoferruginol methyl ether, which was converted into 6β-hydroxyferruginol (37) via deprotection of the methyl group followed by LAH reduction. 6β-Hydroxyferruginol (37) was converted into taxodione (2) and 12-hydroxyabieta-8,11,13-trien-6-one (38). 12-Hydroxyabieta-8,11,13-trien-6-one (38) is not a natural diterpene, but was synthesized for its biological interest.

6. Antibacterial activity of synthesized diterpenes against antibiotic-resistant bacteria

Multiple drug-resistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE), cause serious infections in hospitals worldwide. Antimicrobial compounds against antibiotic-resistant bacteria can be found in natural resources. Many natural phenolic diterpenes show antibacterial activity. The anti-MRSA (664, 730, 996) and anti-VRE (VanA, VanB, VanC) activities of the synthesized phenolic diterpenes and related compounds 32) were examined and revealed 6 compounds with relatively potent activity (Table 1). 11-Hydroxy-12-oxo-

Fig. 7. Syntheses of highly oxidized diterpenes with an abietane skeleton.

| Table 1. Minimum inhibitory concentration (MIC, μg/mL) of synthesized phenolic diterpenes against MRSA and VRE |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| compounds | MRSA | MRSA | MRSA | VanA | VanB | VanC |
| MRSA996 | MRSA730 | MRSA664 | | | |
| 1 | 1 | 1 | 0.5 | 0.5 | 1 | 0.5 |
| 31 | 4 | 4 | 6 | 8 | 8 | 8 |
| 32 | 6 | 6 | 8 | 16 | 16 | 16 |
| 38 | 4 | 4 | 4 | 4 | 6 | 6 |
| 37 | 8 | 8 | 8 | 16 | 16 |
| 2 | 10 | 8 | 8 | 4 | 6 | 4 |
| Vancomycin | 2 | 2 | 256 | 128 | 16 |
| (+)-Ferruginol (16) | | | 125 | 62.5 | | |
| (-)-Ferruginol (22) | | | > 125 | > 125 | | |
| (+)-Ferruginol (23) | | | 62.5 | 31.3 | | |
7,9(11),13-Abietatriene (abietquinone methide, 1) possessed the most potent activity with a minimum inhibitory concentration (MIC) of 0.5-1.0 μg/mL, which is more potent than the activity of vancomycin (Table 1). Taxodione (2, MIC: 4-10 μg/mL) also showed potent activities against both types of bacteria.

The synthetic ferruginol, a well known antibacterial diterpene, racemic (+)-16, natural (+)-22, and unnatural (−)-ferruginol (23), showed weak anti-MRSA and anti-VRE activities.

The results suggest the potential of catechol and quinone methide diterpenes as novel antibacterial compounds. Thus, the facile synthesis of optically active diterpene catechols for further investigation of their various biological activities is planned.

7. Ortho-oxidation of phenols

Many natural diterpene phenols have been isolated from popular plants. Ortho-oxidation of phenols was expected to provide effective synthesis of diterpene catechols from natural diterpene phenols. Benzoyl peroxide (BPO) was used in our first synthesis of abietquinone methide 1, by ortho-oxidation of (±)-ferruginol (15). However, big explosions were reported due to BPO in some industrial plants. We thus planned to use another reagent for the ortho-oxidation reaction. Benzeneseleninic anhydride is known an effective reagent for ortho-oxidation of ferruginol;33) but this reagent was not suitable for the synthesis because of toxicity. Therefore, 2-iodoxybenzoic acid (IBX) was examined for the ortho-oxidation reaction,33) but this reagent was not suitable for the synthesis because of toxicity.

The results suggest the potential of catechol and quinone methide diterpenes as novel antibacterial compounds. Thus, the facile synthesis of optically active diterpene catechols for further investigation of their various biological activities is planned.

![Fig. 8. Oxidation of phenols with mCBPO.](image-url)

**Table 2. Oxidation of phenols with mCBPO.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Phenol</th>
<th>Yield of catechol[α]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-Cresol</td>
<td>n. r.</td>
</tr>
<tr>
<td>2</td>
<td>m-Cresol</td>
<td>35 (4-Me)</td>
</tr>
<tr>
<td>3</td>
<td>p-Cresol</td>
<td>75 (4-Me)</td>
</tr>
<tr>
<td>4</td>
<td>2,3-Xylenol</td>
<td>11 (3,4-diMe)</td>
</tr>
<tr>
<td>5</td>
<td>3,4-Xylenol</td>
<td>39 (3,4-diMe; 4,5-diMe = 1:3)</td>
</tr>
<tr>
<td>6</td>
<td>3,5-Xylenol</td>
<td>33 (3,5-diMe)</td>
</tr>
<tr>
<td>7</td>
<td>2,4-Xylenol</td>
<td>n. r.</td>
</tr>
<tr>
<td>8</td>
<td>3,4,5-Trimethylphenol</td>
<td>56 (3,4,5-tri-Me)</td>
</tr>
<tr>
<td>9</td>
<td>4-Isoproplyphenol</td>
<td>29 (4-iPr)</td>
</tr>
<tr>
<td>10</td>
<td>4-Tert-Butylphenol</td>
<td>17 (4-tBu)</td>
</tr>
<tr>
<td>11</td>
<td>2,4-Di-tert-butylphenol</td>
<td>n. r.</td>
</tr>
</tbody>
</table>

[α] Estimated by 1H-NMR of the diacetate. n.r.: no reaction

mCBPO is stable at high temperatures. In fact, solid mCBPO melts at temperatures higher than 110 °C with foaming when heated in a glass tube. Therefore, reaction of phenols with mCBPO was attempted at the reflux temperature of CH₂Cl₂ and CHCl₃. Phenols were safely oxidized with mCBPO at the reflux temperature in CHCl₃.

7-1. Ortho-oxidation of phenols using mCBPO

Diacylperoxides were synthesized from the corresponding carboxylic acids by treatment with dicyclohexylcarbodiimide (DCC) to form the adduct followed by addition of m-chloroperbenzoic acid (mCPBA) to give asymmetric diacylperoxides (Fig. 8). mCBPO (39) was synthesized from mCBA using a similar procedure.11) The prepared diacylperoxides were examined for suitability for ortho-oxidation of phenols without separation. After the reaction, the mixture was reduced with LiAlH₄ (LAH) and then acetylated with acetic anhydride and pyridine (Table 2). The products were separated for identification and determination of yields. The solution of phenol and mCBPO in CHCl₃ was heated at the reflux temperature for 16 h and then reduced with LAH. The reaction produced catechols from the corresponding phenols with moderate yields. mCBPO (39) crystallized easily from the reaction mixture and was stable under the reaction conditions for ortho-oxidation of phenols to give moderate yields of catechols. mCBPO was synthesized easily from the commercially available peroxide mCPBA. Table 3 shows the stabilities of benzoyl peroxide (BPO) and the chlorinated derivatives. The decomposition temperature and ignition temperature of mCBPO and pCBPO were higher than those of BPO and oCBPO, whereas the heat of decomposition of mCBPO and pCBPO were lower than those of BPO and oCBPO.

These data and the availability of mCBPO prompted its
use as the reagent for ortho-oxidation of phenols. Kubota determined that the explosion of mCBPO in DMF occurred at a temperature higher than 125 °C by differential thermal analysis. Therefore, mCBPO was treated in CH₂Cl₂ or CHCl₃ at the reflux temperature.

8. Syntheses of diterpene catechols from plants constituents

Various diterpene catechols were efficiently synthesized from natural diterpene phenols using the ortho-oxidation reaction described here. Catechol diterpenes can be classified into abietane, totarane, and podocarpane compounds by their carbon skeleton (Fig. 11). The three skeletons have a similar three-ring system, but the abietane skeleton has an isopropyl group at C13, the totarane skeleton has an isopropyl group at C14, and the podocarpane skeleton contains no isopropyl group. Abietaquinoine methide 1 was synthesized first from dehydroabietic acid, which is used as an additive of plastics and paper. Ferruginol (22) was used as an intermediate in the synthesis of 1. After the synthesis, it was discovered that 22 could be obtained efficiently from the resin of the bark of Cryptomeria japonica (Japanese name: sugi). Totarol (42), the starting compound for syntheses of catechols with a totarane skeleton, could be isolated from fresh leaves of Thujaopsis dolabrata (Japanese name: hiba) in about 0.2% yield. Catechols with the podocarpane skeleton were synthesized from ferruginol, 22, by removing the isopropyl group. Details of the syntheses of catechols have been reported previously.

8-1. Syntheses of catechols with a totarane skeleton

Natural totarol (42) was oxidized with mCBPO in CH₂Cl₂ to give an ortho-oxidized catechol ester (43) and its isomer (44) through an ester exchange reaction. The mixture of catechol esters was reduced with LAH to give a catechol (45). Catechol 45 was stable in air and was oxidized with Ag₂O to give an ortho-quinone (46). The ¹H-NMR spectrum showed that the content of ortho-quinone methide 47 was about 1% and that the tautomeric isomerization of 46 to 47 was very slow. The product ratio of 46 and 47 varied (0:100 ~ 1:7) by reaction time and method of silica gel chromatography. The isolated quinone methide 47 was oxidized on silica gel in air to produce maytenoquinone (5). Totarane compounds, catechol 45, quinone 46, and quinone methide 47 were stable in air, at room temperature during column chromatography, and during identification by NMR in CDCl₃. In contrast, the catechol with the abietane skeleton was easily oxidized in air to quinone 46, which was isomerized to abietaquinoine methide (1). The difference in carbon skeleton of totarane and abietane is the position of the isopropyl group, but the stabilities of the catechol, quinine, and quinone methide were very different.

8-2. Syntheses of catechols (52, 53, 56) with a podocarpane skeleton

The podocarpane skeleton contains no isopropyl group on the C-ring, in contrast to the abietane and totarane skeletons. The podocarpane skeleton was prepared from an abietane compound by removing the isopropyl group with ipso-

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**Table 3. Stability of benzoyl peroxide (BPO) and chlorinated derivatives.**

<table>
<thead>
<tr>
<th>Peroxide</th>
<th>Decomposition temp. Initial Peak (°C)</th>
<th>Heat of decomposition (kJ/mol)</th>
<th>Ignition temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPO</td>
<td>107 108</td>
<td>300</td>
<td>106</td>
</tr>
<tr>
<td>mCBPO</td>
<td>112 121</td>
<td>245</td>
<td>114</td>
</tr>
<tr>
<td>oCBPO</td>
<td>89 102</td>
<td>270</td>
<td>87</td>
</tr>
<tr>
<td>pCBPO</td>
<td>129 135</td>
<td>190</td>
<td>127</td>
</tr>
</tbody>
</table>

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![Fig. 9. Synthesis of maytenoquinone.](image-url)
substitution under Friedel-Crafts acylation. Ferruginol methyl ether was treated with AcCl and AlCl₃ to afford nimbose (49) in 73% yield. Nimbose (49) was treated with mCPBA and p-TsOH to give the phenol 51 which was formed by hydrolysis from ester 50, the product of Baeyer-Villiger reaction of 49. Deprotection of the methyl ether of 51 gave podocarpa-8,11,13-triene-12,13-diol (52) with the isomer (53) by a rearrangement. The phenol 51 was converted into dimethyl ether 54, which was oxidized at C-7 (benzylic position) with CrO₃ to give dimethyl ether 55. The dimethyl ether of 55 was treated with BBr₃ to give nimbidiol (56).38)

9. Antimicrobial activity of synthesized diterpene catechols and quinone methides

The antibacterial activities of the diterpene catechols synthesized were examined.37)

Skin diseases such as acne vulgaris are caused by the proliferation of various bacteria, especially *Propionibacterium acnes* and *S. aureus*, on the skin. The lack of effective treatments for skin diseases such as acne vulgaris necessitates the development of new types of antibacterial agents.

Minimum inhibitory concentration (MIC) of the

Fig. 10. Synthesis of nimbidiol.

Fig. 11. Synthesized phenolic diterpenes with an abietane, totarane, or podocarpane skeleton, and related compounds.
synthesized diterpenes, abietane, totarane, and podocarpene compounds were evaluated against *P. acnes* (ATCC 6919) and *S. aureus* ME/GM/TC resistant (ATCC33592) (MRSA). The MICs of ampicillin and vancomycin also were measured as reference compounds against *P. acnes* (ATCC 6919) and MRSA, respectively. Four abietane derivatives (1, 2, 57, 58) and four totarane derivatives (45, 46, 47, 5) showed potent or moderate antibacterial activity against both *P. acnes* and MRSA, whereas podocarpene catechols (61, 52, 53, 56) showed moderate activity (Table 4 and Fig. 11). Diacettes of diterpene catechols possessed less potent antibacterial activity compared to the other catechol derivatives. The MIC (1 μg/mL) of abiestaquinone methide (1) and 8,11,13-totaratriene-12,13-diol (45) was comparable to vancomycin toward *S. aureus* (MRSA). Toxicity of 1 was evaluated by oral dose in mice. No serious change in body weight and behavior of the mice was observed for 7 days after the oral dose of 1000-2000 mg/kg of 1.

In this research, ferruginol (22), the major constituent of the resin of *C. japonica* bark and totarol (42), the major constituent of *T. dolabrata* leaves, readily available starting materials were used for the syntheses. The effective use of these plant resources may help contribute to the preservation of Japanese forests.

### 10. Syntheses of carnosic acid and carnosol, anti-oxidants in rosemary from pisiferic acid

Rosemary is a herb in the *Salvia* family used in cooking and for folk medicines; it contains many anti-oxidant diterpenes.39,40) The German Commission E Monographs consider rosemary extracts effective for treating indigestion and increasing blood circulation. Recently, major antioxidants in rosemary, carnosic acid (64) and carnosol (65), have attracted attention for their neuron-protective effects.41) Many studies have reported biological activities of 64 and 65, such as neuron-protective activity, nerve growth factor forming promoters, and therapeutic agents for amnesia, dementia, Alzheimer's disease, and lipid absorption inhibition.42-44) Carnosic acid is available commercially, but is very expensive (>>$630/500 mg) and is isolated by extraction from natural rosemary. Despite the difficulty of isolating carnosic acid (64) and carnosol (65), no efficient method for synthesizing carnosic acid is available.

*Chamaecyparis pisifera* (Japanese name: sawara) is a tree in Japan with leaves that contain the phenolic diterpene, pisiferic acid (62), as a major constituent.45) Pisiferic acid (62) has an abietane carbon skeleton, and can be described as carnosic acid (64) with a carboxyl group at C-10 and a phenolic hydroxyl group at C-12. Carnosic acid (64) has an additional phenolic hydroxyl group at C11. Therefore, carnosic acid was synthesized from pisiferic acid by ortho-oxidation of the 12-hydroxy group.

Leaves of *C. pisifera* were collected on the Fuchu campus of Tokyo University of Agriculture and Technology. Fresh leaves were extracted with methanol under reflux for 24 h. The extract was evaporated and the residue was extracted with ethyl acetate and water. The organic layer was evaporated and the residue was chromatographed on a short column of silica gel using hexane-ethyl acetate (3:1). Crystallization from ethyl acetate-hexane gave white crystals of pisiferic acid (62). The procedure for the separation of 62 was simple and yielded 62 in about 0.6% based on fresh leaves.

As described above, diterpene catechols were synthesized using ortho-oxidation of phenols with mCBPO. Synthesis of carnosic acid (64) from pisiferic acid (62) was examined first using ortho-oxidation by mCBPO. Pisiferic acid (62) was oxidized with 3 molar equivalents of mCBPO in CH2Cl2 for 16 h at ambient temperature. The crude product 63 was hydrolyzed with sodium hydroxide and sodium borohydride (NaBH4) in methanol. The products were separated by chromatography to give 64 in 11% yield from 62. The spectral properties (’H- and 13C-NMR) of synthetic carnosic acid (64) were identical to those of the natural carnosic acid.39,40) The yield of carnosic acid after oxidation with mCBPO was greater than 50% by 1H-NMR spectroscopy; however, the isolated yield was very low (11%) due to the separation difficulty of 64 from mCBPA (Fig. 12).

Pisiferic acid (62) was then oxidized with 2-iodoxybenzoic acid (IBX) in CHCl3-CH2OH at ambient temperature for 1 h under argon. The product was assumed to be the unstable ortho-quinone, therefore it was reduced by NaBH4 under argon for 4 h without isolation. The 2-iodobenzoic acid was easily crystallized in hexane, the supernatant was evaporated, and the residue was chromatographed to afford 64 in 72% yield from 62 with sequential two step reactions in one pot.

Carnosic acid (64) was then converted to carnosol (65) in 63% yield by oxidation with Ag2O.46,47) This synthesis of carnosic acid (64) has been conducted successfully on a large scale and is now available commercially as a reagent from a Japanese company.

Minimum inhibitory concentrations (MIC) of the synthetic carnosic acid (64) and carnosol (65) were measured against *P. acnes* (ATCC 6919)48) and *S. aureus* ME/GM/TC resistant (ATCC 33592)49) to show the potential of these compounds as

Table 4. Minimum inhibitory concentration (MIC, μg/mL) of synthesized abietane, totarane, and podocarpene diterpenes against *P. acnes*.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MRSA</th>
<th><em>P. acnes</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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</tr>
<tr>
<td>57</td>
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<td>60</td>
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<td>61</td>
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<td>&gt;100</td>
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<td>56</td>
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<td>Vancomycin</td>
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<tr>
<td>Ampicillin</td>
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X: not measured
antibacterial drugs. Both synthetic compounds possessed potent antibacterial activity against \textit{P. acnes} and \textit{S. aureus} (Table 5). The anti-\textit{P. acnes} activity of synthetic carnosic acid (64) (1 \( \mu \)g/mL) was more potent than that of natural carnosic acid (16 \( \mu \)g/mL) as reported by Weckesser.\textsuperscript{50} Because different species of \textit{P. acnes} might have been used in the two studies, comparison of the antibacterial potency of the two carnosic acids is difficult. The isolation and purification of carnosic acid (64) and carnosol (65) from plants are very difficult in general.\textsuperscript{3} Our synthesis affords pure carnosic acid in reasonable yield. The MICs of the antibiotics ampicillin and vancomycin were measured against \textit{P. acnes} (ATCC 6919) and \textit{S. aureus}, respectively, for reference.

The toxicity of pisiferic acid (62) and synthesized carnosic acid (64) was evaluated by providing an oral dose to mice.\textsuperscript{51} No significant change in body weight or behavior of the mice was observed for 7 days after the oral dose of 1000–2000 mg/kg of 64. Pisiferic acid (62) produced slight toxicity after an oral dose of 2000 mg/kg. Because carnosic acid is a constituent of some food items, no serious toxicity was expected. The bioactivities of synthetic carnosic acid (64) are not fully understood and further research needs to be done. Because humans have historically utilized rosemary in various ways, it should have potential as various utilities, \textit{e.g.} an external treatment for acne, cosmetics and nutritional therapies, as well as anti-inflammatory agents, antioxidants, and food additives. Since it is a synthesized natural product, governmental approvals are needed for these applications. The raw material used for production of carnosic acid—the plant \textit{C. pisifera}—is widely distributed in Japan and is easily cultured. Application of these study results may contribute to renewed interest in the forest industry.

### 11. Conclusions

We succeeded efficient syntheses of various diterpenes of abietane, totarane and podocarpane skeletons with catechol, \textit{ortho}-quinone methide or \textit{ortho}-quinone group from easily available plants constituents. Studies of the biological activities of the synthesized catechols, \textit{ortho}-quinone methides and an \textit{ortho}-quinone showed the potential for various utilities of these diterpenes. Since diterpenes are relatively common compounds throughout the plant kingdom, their structures are not novel and cutting-edge reactions for their syntheses are not necessary. However, efficient utilization of plants in the chemical industry is important for realizing a sustainable society, and reducing the dependence of society on petroleum as a raw material.

![Fig. 12. Synthesis of carnosic acid (64) via oxidation with mCBPO.](image1)

![Fig. 13. Syntheses of carnosic acid (64) and carnosol (65) from pisiferic acid (62).](image2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>MRSA</th>
<th>\textit{P. acnes}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnosic acid (64)</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Carnosol (65)</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>
References

17. L. Harrison, Y. Asakawa, Phytochemistry 1987, 26, 1211.
30. J. Gao, G. Han, Phytochemistry 1999, 44, 759.
Introduction of the authors:

Masahiro Tada
Professor Emeritus, Tokyo University of Agriculture and Technology

Masahiro Tada received his Ph.D. from University of Tokyo in March 1974 under the supervision of Professor Takeyoshi Takahashi. From April 1974 to September 1975, he worked as a postdoctoral fellow at University of California, Berkeley with Professor William G. Dauben. Later, he worked as a research fellow of the Japan Society for the Promotion of Science in the Department of Chemistry, University of Tokyo from April 1976 to March 1977. He was promoted to an assistant professor in the Department of Chemistry in April 1977. He then became a lecturer at Tokyo University of Agriculture and Technology in October 1977 and an associate professor in July 1983. In April 1988, he became a professor. He was appointed as a professor at the Institute of Agriculture and Institute of Symbiotic Technology and Science, Tokyo University of Agriculture and Technology in April 2004. He concurrently served as the director of the University Library from April 2001 to March 2003. He retired from the university in March 2009 and was appointed as Professor Emeritus. He continued his research as a professor at Tokyo University of Agriculture and Technology until November 2009. His research fields are organic chemistry and natural product sciences. His research interest includes efficient synthesis of bioactive natural products and creation of novel bioactive substances.

TCI Related Compounds

Carnosic Acid
20mg, 100mg [C2488]
Schreiner et al. have reported the acetalization reaction using 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (1) as a catalyst. Acidic catalysts, such as p-toluenesulfonic acid, are generally needed for acetalization. However, the use of 1 makes it possible to acetalize carbonyl compounds under neutral conditions, affording the corresponding acetal compounds in moderate to high yields.

In particular, 1 is useful for acetalization of carbonyl compounds bearing acid-sensitive groups, such as the TBDMS protecting group.

Reference

Acid-free, organocatalytic acetalization
2-(Bromophenyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborines (1), bromobenzenes bearing a masked boronyl group with 1,8-diaminonaphthalene, were developed by Suginome et al. These masked bromobenzeneboronic acids are useful for oligomer synthesis using the Suzuki–Miyaura cross-coupling reaction. Since the protected boronyl group of 1 is stable under the coupling reaction conditions, the reaction proceeds selectively without the generation of by-products to give the desired coupling products 2 in high yields. The 1,8-Diaminonaphthalene group can be easily removed by simple treatment with aqueous acid, and the resulting boronic acids can be used as substrates of subsequent coupling reactions. Thus, a wide range of functionalized oligoarenes can be synthesized selectively by repeating this coupling reaction of boronic acids with derivatives of 1 and de-protection strategy.

**Typical Procedure: Synthesis of 2a**

To a mixture of the 1a (100 mg, 0.31 mmol), p-tolylboronic acid (42 mg, 0.31 mmol), CsF (94 mg, 0.62 mmol), and Pd[P(t-Bu)3]2 (3.2 mg, 0.0062 mmol) in THF (1.0 mL) is added H2O (0.20 mL) under a nitrogen atmosphere. The mixture is stirred at 60 °C for 11 h. After cooling to room temperature, water is added to the mixture. After extraction with CHCl3, the organic phase is dried over MgSO4 and then filtered through a pad of Celite. Evaporation of the volatile material under vacuum followed by purification by preparative GPC (CHCl3) affords 2a (98 mg, 95%).

**References**

1) Method of synthesizing oligomer compound with cross-coupling reaction
4-tert-Butyl-2,6-dimethylphenylsulfur trifluoride (FLUOLEAD™, 1), which was first reported by Umemoto et al., is a novel nucleophilic fluorinating reagent. Differing from other existing fluorinating reagents, such as DAST, FLUOLEAD™ is a crystalline solid with high thermal stability and less fuming character, which makes it easier to handle. FLUOLEAD™ fluorinates a hydroxy or carbonyl group to afford the corresponding fluorinated compounds in good yields.

Reference
Discovery of 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, and its diverse fluorination capabilities
Recently, there have been many reports on carbon-carbon bond forming processes mediated by \(N\)-heterocyclic carbene (NHC) catalysts. Bode et al. have reported the high-yield and highly enantioselective synthesis of heterocyclic compounds using an NHC precatalyst 2. For example, an NHC \textit{in situ} generated from 2 catalyzes the inverse electron demand Diels–Alder reaction of activated \(\alpha,\beta\)-unsaturated aldehydes with \(\alpha,\beta\)-unsaturated imines to afford the dihydropyridinones with remarkable enantioselectivities.\(^{1a}\)

In case of using \(\alpha\)-chloroaldehydes and \(\alpha,\beta\)-unsaturated ketones, the oxodiene Diels–Alder reaction proceeds to afford the desired products with excellent enatoselectivities, with no more than 0.5 mol\% of the catalyst.\(^{1b}\)

In addition, an achiral precatalyst 3 is also a useful precursor for the NHC-catalyzed redox esterification\(^{2a}\) and amidation\(^{2b}\) of \(\alpha\)-functionalized aldehydes.

*For easier handling, 3 is sold as a perchlorate salt, instead of a chloride salt as reported in the literatures.

References
1) Highly enantioselective Diels–Alder reactions using Bode catalysts
2) \(N\)-Heterocyclic carbene-catalyzed esterification and amidation
IPNBSH (1) is used in the reduction of alcohols to olefins, allenes and ketones under Mitsunobu reaction conditions (Table 1). Treatment of allylic alcohols with 1 forms olefins with the double-bond transposition. 1 is also used in the reduction of alkynyl alcohols and alkyl alcohols to give allenes and alkanes, respectively. Thermal stability of 1 is higher than that of 2-nitrobenzenesulfonyl hydrazide (NBSH), which has been conventionally used. The reduction using 1 can be performed around 0 °C to rt as compared to that using NBSH having to be carried out within −30 to −15 °C. 1 provided greater flexibility with respect to solvent choice, order of addition, and concentration of substrate and reagent. The reaction would proceed the forming of the diazene via the sulfonyl hydrazine, and subsequent loss of dinitrogen to give the reduction products.

Typical Procedure: Synthesis of (E)-3,7,11-trimethyldodeca-1,6,10-triene (Table 1, Entry 1)

Diethyl azodicarboxylate (74 μL, 0.47 mL) is added dropwise to a mixture of IPNBSH (1, 122 mg, 0.474 mmol), trans,trans-fanesol (0.100 mL, 0.393 mmol) and triphenylphosphine (124 mg, 0.473 mmol) in anhydrous THF (9.0 mL) at 0 °C under an argon atmosphere. After 5 min, the reaction mixture is allowed to warm to 23 °C. After 20 min, a mixture of trifluoroethanol and water (1:1, 4.5 mL) is added to the reaction mixture. After 3 h, the reaction mixture is suspended between diethyl ether (25 mL) and water (25 mL), and the aqueous layer is extracted with diethyl ether. The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated. The residue is purified by flash column chromatography on silica gel (eluent: pentane) to give the desired triene (71 mg, Y. 87 %).

Reference

N'-Isopropylidene-2-nitrobenzenesulfonohydrazide (IPNBSH) (1) 5g

Table 1. Reduction of alcohols using IPNBSH

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMeOH</td>
<td>MeMe</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>PhOH</td>
<td>PhMe</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>PhMe</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>MeOCl</td>
<td>MeOCl</td>
<td>87</td>
</tr>
</tbody>
</table>

Typical Procedure: Synthesis of (E)-3,7,11-trimethyldodeca-1,6,10-triene (Table 1, Entry 1)

Diethyl azodicarboxylate (74 μL, 0.47 mL) is added dropwise to a mixture of IPNBSH (1, 122 mg, 0.474 mmol), trans,trans-fanesol (0.100 mL, 0.393 mmol) and triphenylphosphine (124 mg, 0.473 mmol) in anhydrous THF (9.0 mL) at 0 °C under an argon atmosphere. After 5 min, the reaction mixture is allowed to warm to 23 °C. After 20 min, a mixture of trifluoroethanol and water (1:1, 4.5 mL) is added to the reaction mixture. After 3 h, the reaction mixture is suspended between diethyl ether (25 mL) and water (25 mL), and the aqueous layer is extracted with diethyl ether. The combined organic layers are dried over anhydrous sodium sulfate, filtered, and concentrated. The residue is purified by flash column chromatography on silica gel (eluent: pentane) to give the desired triene (71 mg, Y. 87 %).

Reference

N'-Isopropylidene-N'-2-nitrobenzenesulfonyl hydrazine, a reagent for reduction of alcohols via the corresponding monoalkyl diazenes
MTBD (1) and TBD (2) are bicyclic guanidine organic bases. The \( pK_a \) values of the conjugate acids of these bases in acetonitrile are 25 and 26, respectively.\(^1\) 1 and 2 show relatively strong basicities comparing to DBU and TMG (tetramethylguanidine), which are well known as organic bases.

1. Selective Deprotonation of Sulfonamide\(^{2a}\)

\[
\begin{align*}
\text{O} & \quad \text{OBn} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{TBSO} \\
\text{H} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{CO}_2\text{Bn} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OBn} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{TBSO} \\
\text{H} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{CO}_2\text{Bn} \\
\end{align*}
\]

2. Aziridine Ring-Opening Reaction\(^{2b}\)

Instead of DBU and CuOAc, the use of 2 as a base gives better yields (59% to 78%).

\[
\begin{align*}
\text{O} & \quad \text{OBn} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{TBSO} \\
\text{H} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{CO}_2\text{PMB} \\
\end{align*}
\]

3. Wittig, Horner–Emmons Reactions\(^{3}\)

In many cases, the reactions are carried out without anhydrous and inert conditions.

\[
\begin{align*}
R & \quad \text{CH}_2\text{PPh}_3\text{Br}^- \\
O & \quad \text{H} \\
\text{O} & \quad \text{Tolueno, 0 °C} \\
\end{align*}
\]

References
1) Basicity scale in acetonitrile
2) Total synthesis of Ustiloxin D
3) Wittig and Horner–Emmons reactions
B3311  Bromodimethylsulfonium Bromide (1)  5g, 25g

Bromodimethylsulfonium bromide (1) is a brominating reagent for various compounds and its utility has been reported.\(^1\) For example, \(\beta\)-keto esters and 1,3-diketones are brominated smoothly at 0 °C to room temperature to afford the corresponding \(\alpha\)-bromo derivatives selectively in high yields.\(^2\) The notable advantages of this protocol are use of reagent 1, which is less hazardous than molecular bromine, and no added base, Lewis acid, or other catalyst.

Moreover, 1 can be used as a catalyst for protection and de-protection of various functional groups.\(^1\) Recently, a mild Beckmann Rearrangement using 1 has been reported.\(^3\) According to the report, a wide range of ketoximes are converted into the corresponding amides or lactams in high yields.

Typical Procedure: \(\alpha\)-Bromination of \(\beta\)-keto esters and 1,3-diketones\(^2\)

1 (0.278 g, 1.25 mmol) is added to a stirred solution of \(\beta\)-keto ester or 1,3-diketone (1 mmol) in \(\text{CH}_2\text{Cl}_2\) (5 mL) at 0–5 °C or room temperature. After 20 min, the reaction mixture is washed with water (10 mL × 2) and extracted with \(\text{CH}_2\text{Cl}_2\) (10 mL × 2). The organic layers are combined and dried over anhydrous \(\text{Na}_2\text{SO}_4\), and solvents are removed by evaporation in a rotary evaporator to get the crude product.

References
\(^1\) Recent advances in the application of bromodimethylsulfonium bromide in organic synthesis
\(^2\) A mild and regioselective method for \(\alpha\)-bromination of \(\beta\)-keto esters and 1,3-diketones using bromodimethylsulfonium bromide
\(^3\) A mild and efficient catalytic system for Beckmann rearrangement

A Useful Brominating Reagent

A Useful Condensation Activator Bearing Less Nucleophilicity and No Deliquescence

C2421  1-(Cyanomethyl)piperidinium Tetrafluoroborate (1)  5g

Wada *et al.* developed 1-(cyanomethyl)piperidinium tetrafluoroborate (1) conjugates, with a highly less nucleophilic counteranion, BF\(_4\)-.\(^1\) It has appropriate proton-donating ability as a condensation activator to give the corresponding dinucleotide without any loss of the diastereopurity. In addition, the activator has no deliquescence and good solubility in CH\(_3\)CN. Therefore, the activator can be broadly applicable to condensation reactions.

References
\(^1\) Synthesis of oligonucleoside phosphorothioates via the condensation reactions using 1-(cyanomethyl)piperidinium tetrafluoroborate
Selective Fluorination of Hydroxy Group Using DFMBA

D3146  \(N,N\)-Diethyl-\(\alpha,\alpha\)-difluoro-3-methylbenzylamine (= DFMBA) (1) 1g, 5g

\(N,N\)-Diethyl-\(\alpha,\alpha\)-difluoro-3-methylbenzylamine (DFMBA, 1) has two fluorine atoms which can be easily eliminated, and fluorinate hydroxy groups selectively. Hara et al. have reported the fluorination of hydroxy groups in carbohydrates and nucleosides using 1, by which the corresponding fluorinated products are obtained in good yields.\(^1\)

\[ \text{Typical Procedure: Fluorination of 1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose}\]

\[ \text{Into a reactor consisting of a PFA tube with a diameter of 10 mm sealed at one end, are introduced heptane (1 mL), 1 (213 mg, 1 mmol), and 1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose (130 mg, 0.5 mmol). The open end of the reactor is connected to a port in a domestic microwave oven and the port is connected to a reflux condenser located outside the oven. Then, the reaction mixture is submitted to microwave irradiation for 20 min. During the irradiation, the reaction mixture is refluxed vigorously. After the reaction, the reaction mixture is poured into aq. NaHCO}_3 and extracted with ether three times. The combined ethereal layers are dried over MgSO}_4, concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane-ether) gives 6-deoxy-6-fluoro-1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose (Y. 70%).} \]

In addition, Hara et al. have also reported the facile synthesis of heterocyclic and bicyclo compounds by the intramolecular cyclization accompanying the elimination of fluorine groups.\(^2,3\)

References

1)  Selective synthesis of fluorinated carbohydrates using \(N,N\)-diethyl-\(\alpha,\alpha\)-difluoro-(m-methylbenzyl)amine

2)  Facile synthesis of bicyclo orthoesters and bicyclo amide acetals using \(\alpha,\alpha\)-difluoroalkylamines

3)  A facile synthesis of oxazolines, thiazolines, and imidazolines using \(\alpha,\alpha\)-difluoroalkylamines
**Electrophilic Iodinating Reagent**

**I0784**  
*N*-Iodosaccharin (1)  

*N*-Iodosaccharin (1), which was reported by Dolenc, is an effective electrophilic iodinating reagent. 1 is a stable compound, and soluble in common polar organic solvents, such as acetone or acetonitrile. 1 shows higher reactivity and selectivity than other iodinating reagents, such as *N*-iodosuccinimide (NIS), which is frequently used for iodination. For example, 1 reacts smoothly with activated aromatics such as anilines and phenols in good yields. Hydroxy and formyl groups do not react under the reaction conditions.

![Chemical Structure](image)

Moreover, 1 smoothly iodinates alkenes to afford the corresponding adducts of iodine in good yields. It is noted that additions follow the Markovnikov rule with very high regioselectivity. Thus, 1 works as a moderately electrophilic iodinating reagent, which can be used under neutral conditions.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>equiv. of 1</th>
<th>Time (h)</th>
<th>Y. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>OMe</td>
<td>1.05</td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>1.05</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>HO</td>
<td>HO</td>
<td>2</td>
<td>2</td>
<td>83</td>
</tr>
</tbody>
</table>

**Reference**

*N*-Iodosaccharin a new reagent for iodination of alkenes and activated aromatics  
D. Dolenc, *Synlett* 2000, 544.
Air-stable Tri-tert-butyolphosphine Equivalent

T2584  Tri-tert-butyolphosphonium Tetrafluoroborate (1)  1g, 5g

\[
\begin{align*}
\text{MeO}-\text{Br} + (\text{HO})_2\text{B} & \quad \text{Pd}_2(\text{dba})_3 (0.5 \text{ mol\%}) \\
\text{MeO} & \quad \text{Pd}(\text{PhCN})_2\text{Cl}_2 (3 \text{ mol\%}) \\
\text{CuI} & \quad (\text{i-Pr})_2\text{NH} (1.2 \text{ eq.}) \\
\text{dioxane, rt, 2 h} & \quad \text{MeO} \quad \text{Ph} \\
\end{align*}
\]

Y. 98%  Y. 96%

Tri-tert-butyolphosphine is expected to exhibit unusual and unique reactivity different from other phosphine ligands because of its electron-richness and bulkiness. However, tri-tert-butyolphosphine is rather air-sensitive, which makes it difficult to handle. Tri-tert-butyolphosphonium tetrafluoroborate (1) is stable enough to be stored in air for a long period. By using tri-tert-butyolphosphine in situ generated from 1, various kinds of coupling reactions can be demonstrated.

Reference
Air-stable trialkylphosphonium salts

Reagent of the Preparation for Amine-Reactive Water-Soluble Labels

S0836  Sodium 2,3,5,6-Tetrafluoro-4-hydroxybenzenesulfonate (1)  1g, 5g

\[
\begin{align*}
\text{LABEL} & \quad \text{COOH} & \quad \text{DCC, DMF, acetone, rt} & \quad \text{DCC, DMF, acetone, rt} \\
\text{2} & \quad \text{HO} & \quad \text{SO}_3\text{Na} & \quad \text{NH}_2 \\
\text{LABEL} & \quad \text{O} & \quad \text{SO}_3\text{Na} & \quad \text{protein} \\
\text{3} & \quad \text{F} & \quad \text{F} & \quad \text{N} \\
\end{align*}
\]

Sodium 2,3,5,6-tetrafluoro-4-hydroxybenzenesulfonate (1) is a water-soluble active ester synthetic reagent developed by Gee and co-workers. It can convert hydrophobic labeling reagents with carboxyl groups to water-soluble reactive esters under mild conditions. For instance, Suzuki and co-workers synthesized a water-soluble reactive ester (3) from an Hydrophobic fluorescent probe (2) with carboxyl groups by using 1. Amino groups of bovine serum albumin were labeled with 3 in aqueous media. For labeling of biomolecules, 1 is a useful reagent to increase water solubility of hydrophobic labels.

References
1) 4-Sulfotetrafluorophenyl (STP) esters: water-soluble amine-reactive reagents for labeling biomolecules
2) Water-soluble NIR fluorescent probes and their application for protein labeling
K. Umezawa, D. Citterio, K. Suzuki
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