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Ti(III)-Promoted Radical Cyclization of Epoxy Enones. Total Synthesis of (+)-Paeonisuffrone

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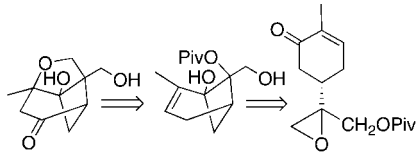

The total synthesis of (+)-paeonisuffrone starting from (+)-10-hydroxycarvone is described. The key step of our synthetic strategy is a titanium-catalyzed stereoselective cyclization initiated by epoxide opening through electron transfer. This reaction stereoselectively affords the highly oxygenated pinane skeleton present in the target molecule and opens a new and effective approach to the synthesis of the complex, biologically active terpenoids isolated from the roots of the Chinese paeony (*Paeonia albiflora* Pallas and *Paeonia suffruticosa* Andrews).

The homolytic opening of epoxides using bis(cyclopentadienyl) titanium chloride (Cp_2TiCl) was first reported in 1988 by Nugent and RajanBabu.[1] Furthermore, the catalytic versions reported by Gansäuer[2] in 1998 and by Oltra[3] in 2003 contributed strongly to extending the scope of radical cyclizations, and the total syntheses of numerous terpenoids in racemic form were reported.[4] However, Cp_2TiCl has found little application in the enantioselective synthesis of natural products.[5] Further applications to intramolecular processes were found by Fernández-Mateos by developing the chemistry of epoxy ketones and epoxy aldehydes,[6] epoxy nitriles,[7] and epoxy esters.[8]

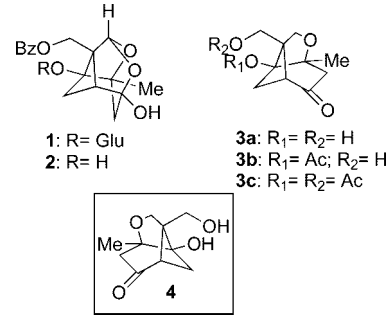

FIGURE 1. Monoterpenes from Chinese paeony.

Moreover, chiral tertiary alcohols are important structural subunits in chemical building blocks and biologically active compounds;[9] for example, (−)-paeoniflorin (**1**), the β-glucoside of paeoniflorigenin (**2**), (−)-paeonisuffrone (**3a**), (−)-paeonisuffrone monoacetate (**3b**), and (−)-paeonisuffrone diacetate (**3c**) are novel complex terpenoids from the roots of the Chinese paeony, *Paeonia albiflora* Pallas and *Paeonia suffruticosa* Andrews (Paeoniaceae),[10] that are widely used in traditional Chinese medicine.[11] They all include a cyclobutyl tertiary alcohol within a compact polyoxygenated structure (Figure 1).

Pioneering synthetic work in this field was reported by Takano,[12] Corey,[13] and Hatakeyama.[14] Furthermore, the total synthesis of (−)-paeonisuffrone (**3a**) was reported by Hatakeyama in 1995. The synthesis of enantiomerically pure **3a** required

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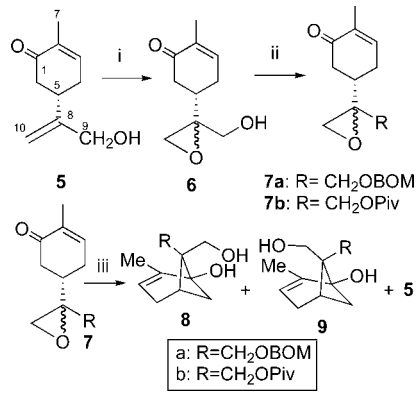
SCHEME 1. Synthesis of Epoxy Enones 7a,b and Ti(III)-Induced Radical Cyclizations[a]



[a] Reactions and conditions: (i) mCPBA, CH_2Cl_2, Na_2CO_3, rt, 15 h, 60%; (ii) *i*Pr_2EtN, $C_6H_5CH_2OCH_2Cl$, THF, 4 days, rt, 85% (for **7a**); ClCO*t*Bu, pyr, CH2Cl2, 15 h, rt, 80% (for **7b**); (iii) Cp_2TiCl_2, Zn, THF rt, 15 h (see Table 1).

TABLE 1. Radical Cyclizations of Epoxy Enones 7a,b[a]

entry	method	starting material	yield (%)[b] **8** + **9**	**8**:**9**[c] ratio	**5** (%)
1	A	**7a**	50	1.1:1	
2	B	**7a**	47	1:1	
3	A	**7a**[d]	45	1:1	
4	A(cat)	**7a**	46	1.2:1	
5	A	**7b**	70	2:1	8
6	B	**7b**	62	1.5:1	15
7	A	**7b**[d]	58	1.75:1	5
8	A(cat)	**7b**	65	2.5:1	6

[a] All reactions were run under an argon atmosphere at room temperature overnight (12 h). In the cases of catalyzed reactions (entries 4 and 8), full conversions were observed after 20 h (**7a**) and 24 h (**7b**). [b] Isolated yields. [c] Determined by either ^{1}H NMR or HPLC. [d] TEA was added as an additive.

the resolution of a racemic intermediate via the *O*-methyl mandelate and unambigously established the absolute configuration of natural paeonisuffrone.[14a]

The synthesis of functionalized pinanes by means of the Ti(III)-promoted radical cyclization of epoxy derivatives of carvone seemed to be an appropriate method to access the polyoxygenated cagelike pinane skeleton present in paeony monoterpenes (**1**−**3**). Here we describe a new synthetic approach to synthesize the highly oxygenated pinane (+)-paeonisuffrone (**4**), the enantiomer of the natural monoterpene (**3a**). Our strategy is based on the Cp_2TiCl-catalyzed reductive C−C bond formation, leading to a tertiary cyclobutyl alcohol after regioselective homolytic epoxide opening of the epoxy pivalate **7b**.

The preparation of (+)-10-hydroxycarvone **5**[15] (Scheme 1) followed by epoxidation and protection of the hydroxy function under basic conditions allowed us to isolate the benzyloxymethyl (BOM) ether **7a** and the pivalate **7b** as mixtures of diastereomers at the C-8 center with 37% and 30% overall yields, respectively, from *S*-(+)-carvone.

We studied the Ti(III)-promoted cyclization reaction of the epoxides **7a,b** under standard conditions (Table 1).[2] Addition of the reagent Cp_2TiCl to the epoxide solution (Method A) afforded a mixture of two diastereomeric alcohols **8a,b** and **9a,b** in moderate yields and low stereoselectivies (the diols **8a,b** were always obtained as the major products in the reaction mixtures).[16] No change in stereoselectivity was observed by reverse addition (Method B), although for the case of **7b** a small increase in the elimination product, **5**, was observed.

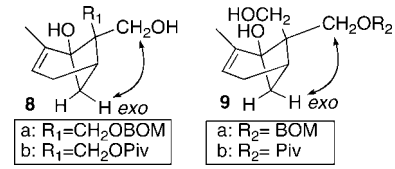


FIGURE 2. Observed ROESY correlations on diols **8a,b** and **9a,b**.

The reaction, which afforded mixtures of diols **8a,b** and **9a,b**, is a chemo- and regioselective radical 4-*exo* cyclization process onto a carbonyl function conjugated with a double bond, as has been observed in previous work carried out at our laboratory.[5d]

The addition of triethylamine to the reaction mixture was performed to suppress the rearranged side products (mostly aldehydes), promoted by Lewis acid catalysis (zinc dihalide) (Table 1, entries 3 and 7).[17] However, under these conditions the stereoselectivities obtained were very similar, but the reaction yields were lower.

The structural assignments of diol diastereomers **8a,b** and **9a,b** were based on complete NMR studies. ROESY experiments were relevant to prove the vicinity between the cyclobutyl *exo* proton and the methylene group belonging to the *exo* side chain present in both types of diastereomers (Figure 2).

The same reaction performed under the catalytic conditions described by Gansäuer[2] yielded higher stereoselectivities but lower yields (Table 1, entries 4 and 8).

The diol **8b** was obtained from the epoxy pivalate **7b** under either stoichiometric or catalytic conditions,[2,3] with similar isolated yields (47% and 46%, respectively), to complete the synthesis of (+)-paeonisuffrone.[18]

Protection of the diol **8b** by treatment with benzaldehyde dimethyl acetal (BDMA) and PPTS afforded the benzylidene acetal **10** in 80% isolated yield (Scheme 2).

Allylic oxidation of **10** was performed by treatment with CrO_3 and dimethyl pyrazole in dichloromethane at −20 °C to afford a mixture of the enone **11** and the benzylic alcohol **12** with 63% yield and 25% isolated yields, respectively.

Conversion of the enone **11** to the paeonisuffrone intermediate **13** required the hydrolysis of the pivalate functionality and conjugate addition (oxa-Michael addition)[19] of the hydroxymethyl side chain to the enone.

Our first effort was performed under the conditions described by Snider on occasion of the biomimetic synthesis of polygalolides A and B by stirring **11** with Cs_2CO_3 in 1:1 THF−H_2O at 50 °C.[20] Unfortunately, no cyclization product was obtained after 7 h of heating the reaction mixture.

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(16) The formation of **5** starting from **7b** would require the activation of an acyloxy elimination step, which is faster than the titanoxy elimination reaction, both triggered off from the same Ti-carbanion intermediate.

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(18) The stoichiometric method required considerable amounts of Cp_2TiCl_2 to obtain acceptable yields of **8c**. Thus, the catalytic method is the best choice for isolating **8c** and carrying out the total synthesis of enantiomerically pure **4**.

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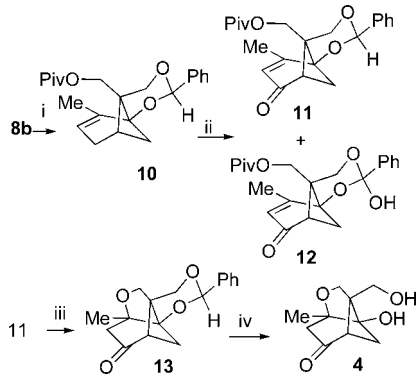
SCHEME 2. Synthesis of (+)-Paeonisuffrone (4)[a]



[a] Reactions and conditions: (i) BDMA, PPTS, CH_2Cl_2, 24 h, 80%; (ii) CrO_3, DMP, CH_2Cl_2, −20°C, 11 (63%), 12 (25%); (iii) 10 N NaOH, CH_3OH, 85%; (iv) H_2, Pd (C), AcOEt, 90%.

However, treatment of a methanolic solution of **11** with aqueous 10 N NaOH at room temperature led to quantitative transformation into the tetracyclic ketone **13**, whose structural assignment was based on complete spectroscopic analysis.

Catalytic hydrogenolysis of **13** with palladium on carbon (5%) led to (+)-paeonisuffrone **4**, with spectroscopic properties identical to those described for the natural enantiomer.[10]

The synthesis of (+)-paeonisuffrone **4** was achieved based on a new strategy that allows access to the functionalized pinane intermediate **8b.** The key step in our strategy was the Ti(III)-catalyzed reductive C−C formation of a cyclobutyl tertiary alcohol after Ti(III)-catalyzed epoxide opening of epoxypivalate **7b**. Transformation of the dihydroxy pivalate **8b** into (+)-paeonisuffrone **4** can be achieved in four steps, with 38% yield.

Experimental Section

Ti-Promoted Cyclization of 7b. *Solution A*: In a 25-mL round-bottomed flask equipped with a magnetic stirrer were placed Zn (195 mg, 3.0 mmol) and Cp_2TiCl_2 (313 mg, 1.25 mmol) under an argon atmosphere. Deoxygenated and freshly distilled tetrahydrofuran (2.5 mL) was added, and the reaction mixture was stirred until the green color persisted. *Solution B*: In a two-necked 25-mL round-bottomed flask equipped with a magnetic stirrer was placed a solution of the epoxy enone **7b** (200 mg, 0.75 mmol) in THF (5 mL) under an argon atmosphere.

Method A. Solution A was added very slowly to solution B, and the reaction mixture was stirred overnight at room temperature.

Method B. Solution B was added dropwise to solution A, and the reaction mixture was stirred overnight at room temperature.

Workup and Isolation of 8b and 9b. When the reaction mixture turned from deep green to red, saturated solutions of NaH_2PO_4 (75 mL) and NaCl (75 mL) were successively added to the reaction mixture. Stirring was maintained for 5 h, and the reaction mixture was filtered. The filtrate was extracted with ether (3 × 25 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed at reduced pressure to yield the crude product. Fractionation of the crude by flash silica gel chromatography eluting with hexane−ethyl acetate (9:1) yielded **8b** (93 mg, 47%), **9b** (46.5 mg, 23%), and **5**[15] (10 mg, 8%) (Method A) and **8b** (75 mg, 37%), **9b** (50 mg, 25%), and **5** (19 mg, 15%) (Method B).

Diol 8b. R_f = 0.60 (hexane−ethyl acetate 1:1); $[\alpha]^{20}_D$ +14.4 (*c* 0.25, $CHCl_3$); IR (film) ν 3418, 2964, 2363, 1726, 1711, 1296, 1172 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.71 (d, J = 9 Hz, 1H), 1.78 (s, 3H), 2.05−2.25 (m, 5H), 2.44 (t, J = 9 Hz, 1H), 3.86 (d, J = 12 Hz, 1H), 4.15 (d, J = 11.5 Hz, 1H), 4.16 (d, J = 12 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 5.30 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.8, 27.7, 29.9, 30.5, 38.9, 39.9, 48.9, 62.9, 64.2, 77.8, 117.6, 145.7, 179.4 ppm. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14, H, 9.01. Found: C, 67.32, H, 9.36. HRMS-EI (M^+ + Na) calcd for $C_{15}H_{24}O_4Na$ 291.1567, found 291.1553.

Diol 9b. R_f = 0.50 (hexane−ethyl acetate 1:1); $[\alpha]^{20}_D$ −26.18 (*c* 0.615, $CHCl_3$); IR (film) ν 3432, 2959, 1716, 1462, 1288, 1165, 1026 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.69 (d, J = 9 Hz, 1H), 1.80 (s, 3H), 1.9−2.4 (m, 5H), 2.41 (t, J = 7 Hz, 1H), 3.51 (d, J =11.3 Hz, 1H), 3,72 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.9 Hz, 1H), 5.31 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.9, 27.2 (3×), 29.9, 30.6, 39.0, 39.9, 50.5, 60. 2, 62.8, 64.4, 117.6, 145.3, 179.5 ppm. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14, H, 9.01. Found: C, 67.38, H, 9.24. HRMS-EI (M^+ + H) calcd for $C_{15}H_{24}O_4$ 269.1747, found 269.1740.

Benzylidene Acetal 10. A solution of **9c** (0.2 g, 0.4 mmol) in 15 mL of dichloromethane was placed in a two-necked 50-mL round-bottomed flask equipped with a magnetic stirrer. Then, benzaldehyde dimethyl acetal (0.3 mL, 0.4 mmol) and pyridinium *p*-toluenesulfonate (cat.) were added under an argon atmosphere, and the reaction mixture was stirred at room temperature for 24 h. When the reaction was finished, a solution of saturated sodium bicarbonate (10 mL) was added, the reaction mixture was extracted with ethyl acetate, the combined organic layers were washed with brine and dried on anhydrous sodium sulfate, and the solvent was removed at reduced pressure to afford a crude (0.5 g), which was fractionated by flash column on silica gel. By elution with hexane−ethyl acetate (95:5), the acetal **10** (0.210 g, 80%) was obtained. R_f = 0.45 (hexane−ethyl acetate 95:5); $[\alpha]^{20}_D$ −75° (*c* 0.60, $CHCl_3$); IR (film) ν 2968, 1728, 1479, 1453, 1393, 1228, 1072, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.59 (d, J = 9 Hz, 1H), 1.81 (s, 3H), 2.1−2.4 (m, 5H), 3.24 (t, J = 9 Hz, 1H), 4.22 (d, J = 12 Hz, 1H), 4.23 (d, J = 12 Hz, 1H), 4.33 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 12 Hz, 1H), 5.32 (s, 1H), 5.93 (s, 1H), 7.36 (m 3H), 7.50 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 16.4, 27.2 (3×), 30.1, 30.5, 32.4, 38.9, 41.1, 62.8, 70.2, 96.1, 117.5, 126.3, 128.1, 128.8, 138.5, 144.1, 178.6 ppm. Anal. Calcd for $C_{22}H_{28}O_4$, C, 74.13, H, 7.92. Found: C, 74.37, H, 8.16. HRMS-EI (M^++ Na) calcd for $C_{22}H_{28}O_4Na$ 379.1880, found 379.1883.

Enones 11 and 12. A suspension of chromium oxide (1.15 g, 12 mmol) in dry dichloromethane (25 mL) was placed in a two-necked 50-mL round-bottomed flask equipped with a magnetic stirrer. The reaction mixture was cooled to −20 °C, and dimethylpyrazole (1.1 g, 12 mmol) was added in one portion under an argon atmosphere. After 15 min a solution of the acetal **10** (0.36 g, 1mmol) in dichloromethane (20 mL) was added dropwise, and the reaction mixture was stirred for 4 h, maintaining the temperature between −10 and −20 °C. A sodium hydroxide solution (2 mL, 5 N) was then added, and the reaction mixture was stirred at 0 °C for 1 h. The two phases were separated, and the combined organic layers were washed with dilute hydrochloric acid to remove the DMP. The organic layers were washed with a saturated NaCl solution, dried over Na_2SO_4, and evaporated at reduced pressure to afford a crude product (0.4 g), which was fractionated by flash chromatography on silica gel. By elution with hexane−ethyl acetate (8:2), the enones **11** (233 mg, 63%) and **12** (93 mg, 25%) were isolated. **Enone 11:** R_f = 0.50 (hexane−ethyl acetate 8:2); $[\alpha]^{20}_D$ = −84.4 (*c* 0.97 $CHCl_3$); IR (film) ν 2960, 2923, 2853, 1728, 1688, 1457, 1227 cm^{-1}; UV (EtOH) λ_{max} = 205 (ε 12024); λ_{max} = 254 nm (ε 4780). ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 2.10 (s, 3H); 2.46 (d, J = 10 Hz, 1H); 2.81 (d, J = 5 Hz, 1H); 3.68 (dd, J_1 = 5 Hz, J_2 = 10 Hz, 1H); 4.23 (d, J = 12 Hz, 1H), 4.40 (d, J = 12 Hz, 1H), 4.46 (s, 2H), 5.79 (s, 1H), 6.02 (s, 1H), 7.39 (m, 3H); 7.49 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 17.5, 27.1 (3×), 38.9, 42.4, 46.4, 54,6, 63.0, 69.8, 96.7, 121.1, 126.2, 128.3, 129.2, 137.3, 169.1, 178.2, 198.6 ppm. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33, H, 7.07. Found: C, 71.52, H, 7.34. HRMS-EI (M^++ Na) calcd for $C_{22}H_{26}O_5Na$ 393.1672, found 393.1667. **Enone 12:** Mp 160−161 °C. R_f = 0.25 (hexane−ethyl acetate 8:2); $[\alpha]^{20}_D$ = −31.22 (*c* 0.6 $CHCl_3$); IR (film) ν 3441, 2970, 2921, 1725, 1677, 1271 cm^{-1}. ^1H

NMR ($CDCl_3$) δ 1.18 (s, 9H), 2.14 (s, 3H), 2.60 (d, J = 9 Hz, 1H), 2.93 (m, 2H), 4.13 (d, J = 12 Hz, 1H), 4.43 (d, J = 12 Hz; 1H), 4.67 (d, J = 12 Hz 1H), 4.83 (d, J = 12 Hz, 1H), 5.81 (s, 1H), 7.46 (m, 2H), 7,58 (m, 1H), 8.02 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 18.3, 27.1 (3×), 38.9, 46.6, 48.1, 62.8 (2×), 62.9, 77.6, 121.1, 128.5, 129.3, 129.7, 133.5, 166.8, 171.1, 178.1, 199.5 ppm. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38, H, 6.78. Found: C, 68.52, H, 6.96. HRMS-EI (M^++ Na) calcd for $C_{22}H_{26}O_6Na$ 409.1622, found 409.1617.

Tetracyclic Ketone 13. A solution of **11** (0.185 g, 0.5 mmol) in methanol (2 mL) was placed in a two-necked 50-mL round-bottomed flask equipped with a magnetic stirrer. Sodium hydroxide (0.01 mL, 10N) was added and the reaction mixture was stirred for 24 h at room temperature. Evaporation of the solvent was followed by the addition of water (5 mL) and extraction of the aqueous phase with dichloromethane. The organic layers were washed with saturated sodium chloride and dried on anhydrous sodium sulfate to yield a crude product (0.17 g), which was fractionated by flash chromatography on silica gel. By elution with hexane−ethyl acetate (8:2) the tricyclic ketone **13** (0.122 g, 85%) was isolated. R_f = 0.50 (hexane−ethyl acetate 8:2); $[\alpha]^{20}_D$ = +0.88 (c 1.13, $CHCl_3$); IR (film) ν 2960, 2924, 2855, 1729, 1144, 1014 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3H), 2.14 (d, J = 12 Hz, 1H), 2.59 (d, J = 18 Hz, 1H), 2.80 (d, J = 7 Hz, 1H) 2.85 (d, J = 18 Hz, 1H), 3.13 (dd, J_1 = 7.0 Hz, J_2 = 12 Hz, 1H), 3.87 (d, J =10 Hz, 1H), 4.15 (d, J =10 Hz, 1H), 4.16 (d, J = 12 Hz, 1H), 4.31 (d, J = 12 Hz, 1H), 5.88 (s, 1H), 7.39 (m, 3H), 7.54 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 18.1, 25.2, 49.0, 49.1, 51.8, 68.2, 70.7, 79.8, 86.7, 96.8, 126.4, 128.3, 129.3, 137.4, 208.3 ppm. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31, H, 6.34. Found: C, 71.56, H, 6.58. HRMS-EI (M^++ Na) calcd for $C_{17}H_{18}O_4Na$ 309.1097, found 309.1091.

(+)-Paeonisuffrone 4. Palladium on carbon (5%) was suspended in ethyl acetate (2 mL) in a two-necked 50-mL round-bottomed flask equipped with a magnetic stirrer. A solution of **13** (0.143 g, 0.5 mmol) in ethyl acetate (1.5 mL) was added dropwise, and the reaction mixture was stirred under hydrogen for 4 h. at room temperature. Filtration of the reaction product through celite and evaporation of the solvent afforded **4** (0.09 g, 90%). Mp 163−164 °C. R_f = 0.50 (hexane−ethyl acetate 1:1); $[\alpha]^{20}_D$ = +17.34°(c 0.8, CH_3OH); IR (film) ν 3372, 1727, 1458, 1240, 1166, 1052, cm^{-1}. ^{1}H NMR (CD_3OD) δ 1.31 (s, 3H), 2.20 (d, J =11 Hz, 1H), 2.31 (d, J =18 Hz, 1H), 2.46 (dd, J_1 = 7 Hz, J_2 =11 Hz, 1H), 2.85 (d, J = 7 Hz, 1H) 2.91 (d, J =18 Hz, 1H), 3.57 (d, J = 10 Hz, 1H), 3.83 (d, J = 12 Hz, 1H), 3.88 (d, J = 10 Hz, 1H), 3.89 (d, J_1 = 12 Hz, 1H) ppm. ^{13}C NMR (CD_3OD) δ 19.2, 31.7, 49.5, 49.8, 62.7, 63.0, 71.7, 82.2, 87.6, 212.9 ppm. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59, H, 7.12. Found: C, 60.72, H, 7.30. HRMS-EI (M^++ Na) calcd for $C_{10}H_{14}O_4Na$ 221.0784, found 221.0787.

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Supporting Information Available: Experimental procedures for the preparation and characterization of **6**, **7a**, **7b**, **8a**, and **9a** and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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