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Tetrahedron
Tetrahedron 60 (2004) 1581–1585

Formal synthesis of (±)-udoteatrial hydrate

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Received 31 October 2003; accepted 1 December 2003

Abstract—The formal synthesis of antimicrobial diterpene udoteatrial hydrate (**1**) is described in nine steps. Diol **6** used as starting material. The key intermediate **4** was obtained from bicyclic ketone **5** via the key Norrish type I reaction.

1. Introduction

The synthetic studies for highly oxygenated polycyclic acetals and lactones have provided various approaches toward molecules, such as udoteatrial hydrate,[1] bilobalide,[2] ginkgolide A and B,[3] gracilin B and C,[4] and specionin.[5] In this report, we describe the formal synthesis of udoteatrial hydrate (**1**), which has an 'udoteane' carbon skeleton with all *cis* substituents relationship on the cyclopentane ring and a geranyl side chain. This unusual monocyclic diterpenoid trialdehyde udoteatrial is isolated from the calcareous marine green algae *Udotea flabellum* has existed in a mono-hydrate form and showed antimicrobial activities against *Staphylococcus aureus* and *Candida albicans* (Fig. 1).[1e]

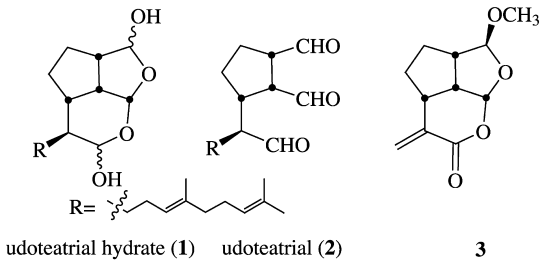


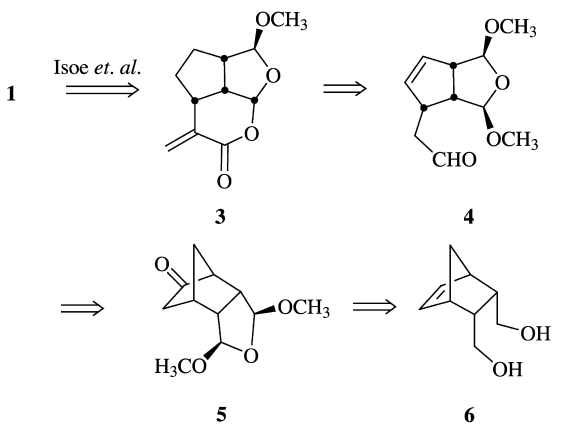
Figure 1. Structure of udoteatrial hydrate (**1**), udoteatrial (**2**) and **3**.

To date, there are only two reports for the total synthesis of udoteatrial hydrate citations. In 1983, Whitesell and his co-workers reported the racemic synthesis of udoteatrial hydrate using the Claisen rearrangement and zirconium-catalyzed carboalumination as key steps. In 1993, Isoe and his co-workers[1b,c] described an asymmetrical synthesis of the antipode of udoteatrial hydrate using genipin as a building block. The tricyclic *exo*-methylene lactone with *cis*-fused ring junction and contiguous stereogenic centers were designated to be a key intermediate. The geranyl side chain was introduced into the iridoid carbon framework thermodynamically.

2. Results and discussion

Recently, we found that bicyclo[2.2.1]heptanone can undergo the Norrish type I reaction[6] to afford the corresponding *cis*-trisubstituted cyclopentenoid compound. We applied this approach in the synthesis of natural products, such as pedicularis-lactone,[7a] ningpogenin,[7a] boschnialactone,[7b] and iridolactone.[7c]

The methodological studies we have carried out to date have left addressed a pertinent issue, which impacts the general applicability of the method to give access to a wide range of



Scheme 1. Retrosynthetic study of udoteatrial hydrate (**1**).

Keywords: Udoteatrial hydrate; Bicyclo[2.2.1]heptanone; Norrish type I reaction.
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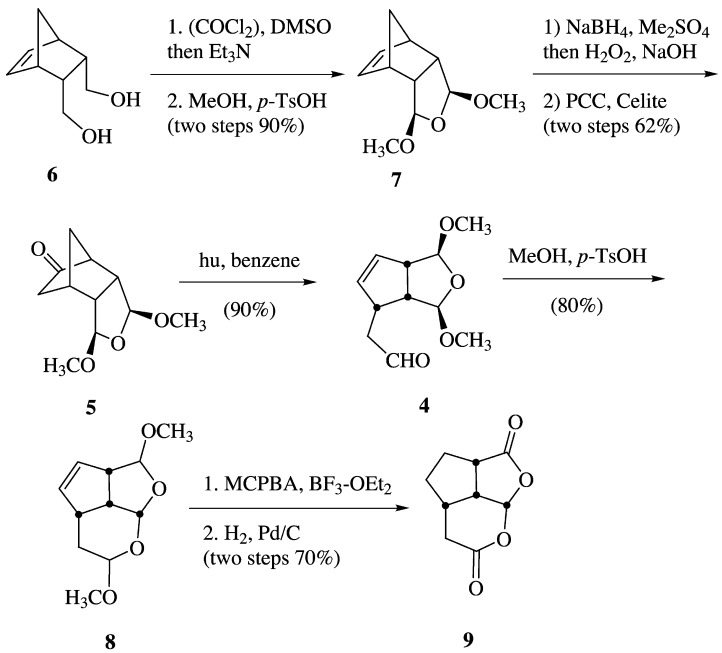
doi:10.1016/j.tet.2003.12.014



Scheme 2. Synthesis of tricyclic lactone **9**.

related targets. With respect to the previous results, we describe the application of this Norrish type I reaction to the formal synthesis of **1**. The retrosynthetic strategy is illustrated in Scheme 1. The target, Isoe's key intermediate **3**, was synthesized from aldehyde **4**, which in turn was derived from the Norrish type I reaction of ketone **5**. The functional group transformation of diol **6** was performed in a straightforward reaction involving oxidation, protection and hydroboration reactions.

The formal synthesis of udoteatrial hydrate (**1**), as shown in Scheme 2, uses a facile strategy from diol **6**. Diol **6** was readily obtained from cyclopentadiene in two-step reactions of the Diels–Alder cycloaddition with maleic anhydride and reduction with lithium aluminum hydride. Swern oxidation of diol **6** produced the resulting dialdehyde. Without further purification, treatment of the dialdehyde with methanol containing a catalytic amount of *p*-toluenesulfonic acid caused cyclization to give the sole compound **7**. Treatment

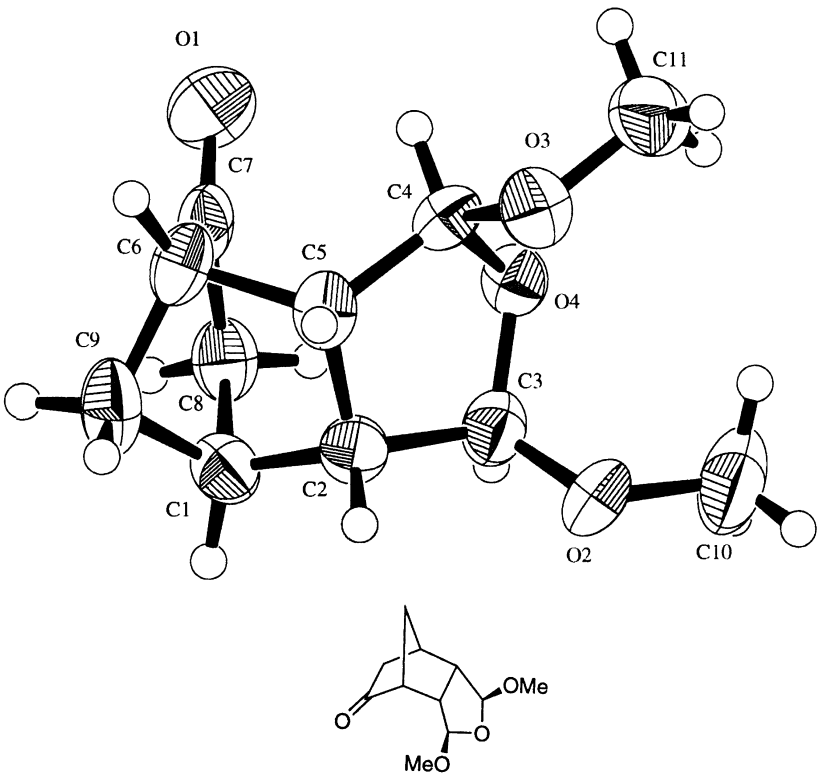


Diagram 1. X-ray crystallography of **5**.

of **7** with a mixture of sodium borohydride and dimethyl sulfate, followed by oxidative work-up led to the alcohol as a single stereoisomer.[7a] The alcohol then reacted with pyridinium chlorochromate to give the corresponding bicyclo[2.2.1]heptanone **5**. The structure of **5** was determined by single-crystal X-ray analysis (Diagram 1).

The key intermediate, trisubstituted cyclopentenoid **4**, was obtained in high yield via photolytic cleavage (λ>310 nm) of the bicyclo[2.2.1]heptanone **5** in methanol for 15 h. The sole tricyclic product **8** was generated in one efficient cyclization by the treatment of **4** with methanol under mild acidic condition.

With compound **8** in hand, we focused on the alkylation at the α-position of the six-membered ring on the tricyclic skeleton. Tricyclic compound **8** was oxidized with *m*-chloroperoxybenzoic acid to yield the unstable bis-lactone catalyzed with boron trifluoride etherate.[2a] Without further purification, the unsaturated bis-lactone was hydrogenated to yield saturated bis-lactone **9** in ethyl acetate. Unfortunately, when **9** was treated with base, such as sodium hydride, lithium diisopropylamide, or potassium *t*-butoxide, to generate the anion for the alkylation, the complex products produced. Since bis-lactone **9** did not survive at basic condition, an alternative approach forward Isoe's intermediate **3** was investigated (Scheme 3). Hydrogenation of the unsaturated **4** catalyzed with palladium on activated carbon in methanol gave the corresponding saturated product, which was followed by the reaction with a mixture of dibromomethane and diethylamine yielded α-methylene product **10**.[8] Next, we examined the oxidation of **10** using variety oxidants, such as ruthenium tetraoxide, silver oxide and Jones reagent, but the desired acid was not obtained. Finally, oxidation of **10** with sodium chlorite successfully yielded the corresponding acid which was further reacted with a catalytic amount of boron trifluoride etherate to produce the tricyclic lactone **3**.

3. Conclusion

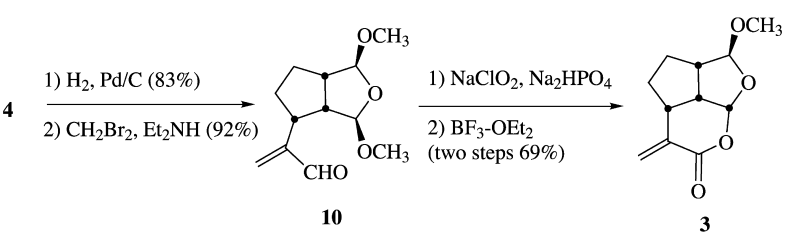
In conclusion, the successful synthesis of tricyclic lactone **3** demonstrates the utility of the Norrish type I reaction on a bicyclo[2.2.1]heptanone skeleton for the formal synthesis of udoteatrial hydrate (**1**). Efforts directed toward the synthesis of other naturally occurring iridoids are currently under way in our laboratory.

4. Experimental

4.1. General

THF and benzene were distilled before use from a deep blue solution resulting from sodium and benzophenone under nitrogen All reagents and solvents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) analysis was performed with precoated silica gel (60 f_{254} plates) and column chromatography was carried out on silica (70–230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those in aqueous solutions) spherical flasks and stirred with magnetic bars. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo. ^{1}H NMR spectra were determined at 300 or 500 MHz, and ^{13}C NMR spectra were determined at 75 or 125 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques.

4.1.1. *cis-endo*-3,5-Dimethoxy-4-oxa-tricyclo[5.2.1.0^{2,6}]-dec-8-ene (7). A solution of oxalyl chloride (17.74 g, 12.0 mL, 139.8 mmol) in dichloromethane (80 mL) at −78 °C, and dimethyl sulfoxide (20.35 g, 18.5 mL, 260.5 mmol) were added carefully. The solution was warmed to −40 °C for 5 min and recooled to −78 °C, and then a solution of alcohol (5.1 g, 32.5 mmol) in dichloromethane (15 mL) was added dropwise for 20 min followed by excess triethylamine (45 mL) for 30 min. The reaction mixture was warmed to room temperature and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce the crude compound. Without further purification, a mixture of crude dialdehyde and *p*-toluenesufonic acid (10 mg) in methanol (40 mL) was stirred for 3 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×40 mL) and water (10 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 4:1) produced compound **7** (7.0 g, 90%) as a colorless oil. IR ($CHCl_3$) 1642 cm^{-1}. EI-MS $C_{11}H_{16}O_3$ *m/z* (%)=196 (M^+, 1), 164 (54), 130 (96), 99 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1108; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (t, *J*=1.9 Hz, 2H), 4.50 (s, 2H), 3.32 (s, 6H), 2.99–2.97 (m, 2H), 2.92–2.90 (m, 2H), 1.42 (AB, *J*=8.4 Hz, 1H), 1.30 (AB, *J*=8.4 Hz, 1H); ^{13}C



Scheme 3. Synthesis of Isoe's intermediate (**3**).

NMR (75 MHz, $CDCl_3$) δ 134.46, 108.80, 54.80, 53.45, 51.36, 44.68.

4.1.2. *cis-endo*-3,5-Dimethoxy-4-oxa-tricyclo[5.2.1.0^{2,6}]-decan-8-one (5). To a mixture of olefin **7** (4.33 g, 22.1 mmol) and sodium borohydride (1.05 g, 26.5 mmol) in THF (60 mL) was added carefully dimethyl sulfate (2.3 mL, 3.06 g, 24.3 mmol) in THF (40 mL) in an ice bath. The mixture was stirred at room temperature for 2 h. Oxidation was carried out by dropwise addition of hydrogen peroxide solution (35%, 20 mL)/3 N sodium hydroxide (10 mL)/water (10 mL) (vol.=2/2/1). The mixture was held an additional 1 h at reflux temperature, cooled and extracted with ethyl acetate (3×30 mL). After separation, the organic layers were dried, filtrated and evaporated to yield the crude alcohol. The crude alcohol in dichloromethane (40 mL) was added to a mixture of pyridinium chlorochromate (7.2 g, 34.9 mmol) and Celite (10 g) in dichloromethane (60 mL). After being stirred at room temperature for 4 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was dried, filtered and concentrated to produce crude ketone. Purification on silica gel (hexane/ethyl acetate, 2:1) afforded **5** (2.9 g, 62%) as a solid. Mp 76–78 °C; IR ($CHCl_3$) 1745, 1641 cm^{-1}; EI-MS $C_{11}H_{16}O_4$ *m/z* (%)=212 (M^+, 1), 181 (41), 152 (78), 110 (93), 79 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.62 (s, 1H), 3.32 (s, 6H), 2.77–2.73 (m, 2H), 2.62 (br s, 1H), 2.55–2.53 (m, 1H), 1.87–1.83 (m, 2H), 1.59–1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.91, 107.19, 107.13, 55.41, 55.17, 53.38, 51.77, 49.60, 40.21, 39.55, 36.46. Crystal of **5** was grown by slow diffusion of ethyl acetate into a solution of **5** in dichloromethane to yield the prism: primitive orthorhombic, a=19.096(4) Å, b=10.829(3) Å, c=10.430(4) Å, V=2157.0(9) Å^3, Z=8, d_{calcd}=1.307 g/cm^3, F(000)=912.00, 2θ range 25 (16.8–23.0°).

4.1.3. (1,3-Dimethoxy-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)acetaldehyde (4). Ketone (0.2 g, 0.94 mmol) dissolved in benzene (200 mL) free of oxygen was irradiated under a nitrogen atmosphere with a UV lamp (λ>310 nm), using a pyrex glass filter at room temperature for 15 h. The solvent was evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate, 4:1) afforded **4** (0.18 g, 90%) as a solid: IR ($CHCl_3$) 1707, 1639 cm^{-1}; EI-MS $C_{11}H_{16}O_4$ *m/z* (%)=212 (M^+, 1), 181 (20), 149 (43), 108 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (t, J=1.4 Hz, 1H), 5.77–5.63 (m, 2H), 4.88 (d, J=2.1 Hz, 1H), 4.87 (s, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.05 (td, J=1.8, 8.1 Hz, 1H), 2.72 (ddd, J=1.5, 6.9, 15.6 Hz, 1H), 2.58 (ddd, J=1.5, 6.9, 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.71, 134.98, 130.17, 109.59, 108.49, 57.85, 55.48, 55.19, 49.82, 45.47, 40.56.

4.1.4. 2,6-Dimethoxy-2a,4a,5,6,7a,7b-hexahhydro-2*H*-1,7-dioxacyclopenta[*cd*]indene (8). A mixture of aldehyde **4** and *p*-toluenesufonic acid (10 mg) in methanol (40 mL) was stirred for 8 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×10 mL) and water (5 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 5:1) produced compound **8** (80 mg, 80%) as a colorless oil: IR ($CHCl_3$) 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.63 (m, 2H), 4.77 (s, 1H), 4.64 (dd, J=2.7, 8.7 Hz, 1H), 3.47 (s, 3H), 3.39 (s, 3H), 3.50–3.34 (m, 2H), 3.22–3.18 (m, 1H), 2.87–2.80 (m, 1H), 1.90–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.98, 129.98, 104.96, 101.83, 95.64, 58.28, 55.90, 54.74, 41.29, 36.92, 30.95.

4.1.5. Perhydro-1,7-dioxafuro[1,2,3-*cd*]isobenzofuran-2,6-dione (9). To a solution of *m*-chloroperoxybenzoic acid (860 mg, 5.0 mmol) in dichloromethane (10 mL) and diethyl ether (1 mL) at rt was added boron trifluoride etherate (1 M, 2.1 mL, 2.1 mmol). The solution was heated to 60 °C for 10 min, and then a solution of **8** (150 mg, 0.7 mmol) in dichloromethane (5 mL) was added dropwise for 5 min. The reaction mixture was reacted at reflux temperature for 2 h. And the mixture was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate solution (3 mL). The organic layers were washed with aqueous sodium bicarbonate solution (10 mL) and then dried, filtered and evaporated. Without further purification, the unstable product (100 mg) in ethyl acetate (10 mL) was stirred under 1 atm of hydrogen at room temperature with 10% palladium on activated carbon as catalyst (10 mg) for 2 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the desired crude compound. Purification on silica gel (hexane/ethyl acetate, 1:1) produced tricyclic bislactone **9** (92 mg, 72%) as a colorless solid: mp 99–100 °C; IR ($CHCl_3$) 1770, 1130 cm^{-1}; HRMS (EI, M^++1) calcd for $C_9H_{11}O_4$ 183.0657, found 183.0657; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J=6.6 Hz, 1H), 3.40–3.20 (m, 2H), 2.75–2.56 (m, 2H), 2.35–2.21 (m, 3H), 2.10–1.95 (m, 1H), 1.70–1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.39, 167.84, 99.46, 45.34, 42.27, 36.16, 32.70, 32.35, 28.06. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.74.

4.1.6. (1,3-Dimethoxy-hexahydro-cyclopenta[*c*]furan-4-yl)-acetaldehyde (10). Olefin **4** (0.38 g, 1.79 mmol) was dissolved in ethyl acetate (10 mL) and 10% palladium on activated carbon as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the desired saturated compound (0.31 g, 83%): IR ($CHCl_3$) 1739 cm^{-1}; FAB-MS $C_{11}H_{18}O_4$ *m/z* (%)=213 (M^++1, 10), 199 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.75–2.63 (m, 3H), 2.51–2.35 (m, 2H), 1.76–1.74 (m, 2H), 1.64–1.60 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.09, 113.07, 107.83, 55.31, 54.95, 52.34, 49.09, 45.51, 36.15, 30.93, 29.40. A solution of resulting aldehyde (200 mg, 0.93 mmol) was added to a mixture of diethylamine (200 mg, 2.8 mmol) and dibromomethane (10 mL) and the reaction mixture was heated to 55 °C for 2 h and cooled to room temperature. The reaction mixture was evaporated and purified on silica gel (hexane/ethyl acetate, 4:1) to produce olefin **10** (194 mg, 92%) as a colorless oil: IR ($CHCl_3$) 1648 cm^{-1}; EI-MS $C_{12}H_{18}O_4$ *m/z* (%)=225 (M^++1, 1), 195 (93), 134 (100); HRMS (EI, M^+) calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1212; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 6.30 (s, 1H), 6.17 (s, 1H), 4.78 (s,

1H), 4.48 (s, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.07 (t, J=7.5 Hz, 1H), 2.94 (m, 1H), 2.84 (t, J=8.0 Hz, 1H), 1.84–1.70 (m, 3H), 1.55–1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.09, 150.17, 134.17, 113.65, 108.88, 55.17, 54.99, 50.56, 49.10, 41.08, 29.13, 27.55.

4.1.7. 2-(1,3-Dimethoxy-hexahydro-cyclopenta[*c*]furan-4-yl)-propenal (3) (Isoe's intermediate). A solution of aldehyde **10** (100 mg, 0.44 mmol) and 2-methyl-2-butene (chlorine scavenger) (1 mL) in *t*-butanol (10 mL) was treated with a solution of sodium chlorite (80%, 550 mg, 5.0 mmol) and potassium dihydrogen phosphate (KH_2PO_4, 600 mg) in water (5 mL) at room temperature. The mixture was stirred for an additional 30 min, then the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3×10 mL) and water (5 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated to yield the crude product. Without further purification, boron trifluoride etherate (1 M, 0.1 mL) was added to a solution of the resulting product (90 mg) for 4 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×10 mL) and water (5 mL). The organic layers were washed with aqueous sodium bicarbonate solution (10 mL) and then dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 5:1) produced compound **3** (64 mg, 69%) as a colorless oil: IR ($CHCl_3$) 2950, 1735, 1630 cm^{-1}; HRMS (EI, M^+ +1) calcd for $C_{11}H_{15}O_4$ 211.0970, found 211.0965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (t, J=1.0 Hz, 1H), 5.84 (d, J=6.5 Hz, 1H), 5.57 (t, J=1.0 Hz, 1H), 4.87 (d, J=2.5 Hz, 1H), 3.43 (s, 3H), 3.16–3.00 (m, 2H), 2.77–2.69 (m, 1H), 1.91–1.82 (m, 2H), 1.80–1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.18, 136.44, 125.38, 110.52, 102.83, 56.16, 50.65, 45.68, 42.00, 33.65, 29.15.

5. Supplementary material

Additional spectroscopic data for compounds **3**–**5**, **7**–**10** (^{1}H NMR in $CDCl_3$).

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for financial support.

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