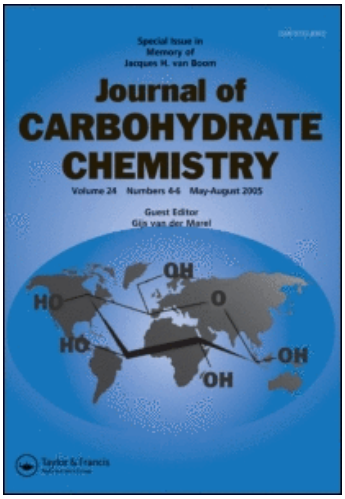

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Synthesis and Application of 3,3-Spirocyclopropane Derivatives Obtained from 1,2:5,6-Di-*O*-Isopropylidene-α-D-Glucofuranose

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SYNTHESIS AND APPLICATION OF 3,3-SPIROCYCLOPROPANE DERIVATIVES OBTAINED FROM 1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-D-GLUCOFURANOSE[1]

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ABSTRACT

3,3-Spirocyclopropane derivatives (**5** and **7**) were prepared by three different methods of cyclopropanation starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**). Subsequent radical induced cyclopropane ring opening reaction stereospecifically provided the 3-*C*-allyl derivative (**9**). However, activation of the cyclopropyl ring through the aldehyde (**10**) followed by hydrogenation gave a quaternary chiral derivative (**11**) which was elaborated to the versatile intermediate (**1**) by using Bamford-Stevens reaction.

INTRODUCTION

It is widely known that carbohydrates incorporating quaternary chiral centres are useful synthons for natural products synthesis.[2] Introduction of a quarternary centre in a carbohydrate substrate is a challenging endeavour. The Claisen orthoester rearrangement is the most commonly used strategy to generate stereogenic quaternary centres in both pyranose and furanose substrates.[3]

In developing an alternate and complimentary methodology for constructing a quaternary centre, we rationalised[4] that spirocyclopropane sugar derivatives might be

useful synthons because cyclopropane ring systems undergo facile nucleophilic, electrophilic and radical ring opening reactions via different pathways and releasing the inherent strain in the molecule.[5] In this communication, we report the new synthesis of sugar spirocyclopropane derivatives and their applications. As a representative example, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-vinyl-α-D-allofuranose (**1**) has been identified (Figure 1) as a versatile synthon for natural product synthesis.[6]

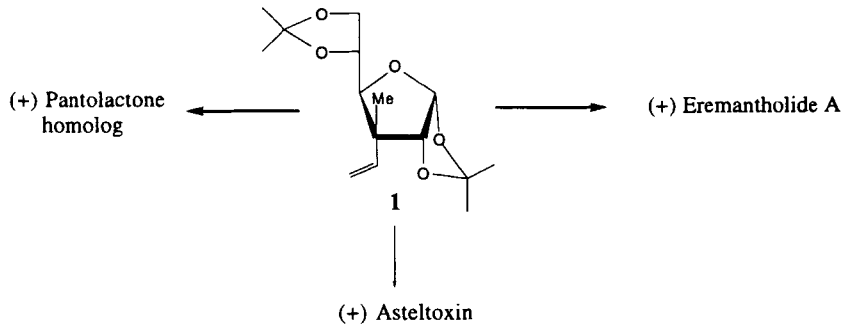
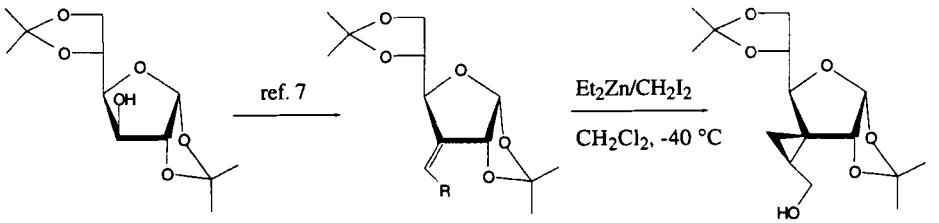


Figure 1. Application of **1** in natural product synthesis

RESULTS AND DISCUSSION

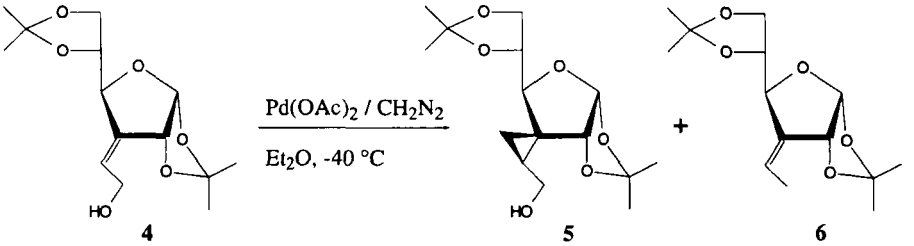
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) was converted into the allylic alcohol **4** *via* the corresponding α, β-unsaturated ester **3** in good yield.[7] The modified Simmons-Smith reaction[8] with CH_2I_2/Et_2Zn in CH_2Cl_2 at -40 °C gave a single stereogenic spirocyclopropane derivative **5** in 80% yield. Although the configuration at C-3 of **5** could not be established from its ^1H NMR spectrum, further chemical modifications unequivocally proved the correct structure to be as shown. The exclusive formation of **5** was attributed to the stereocontrolling effect of 1,2-*O*-isopropylidene group (Scheme 1). We felt it would be interesting to explore other cyclopropanation protocols and promote reverse stereochemical induction in the substrate **4**.



2 **3** R = CO_2Et; **4** R = CH_2OH **5**

Scheme 1

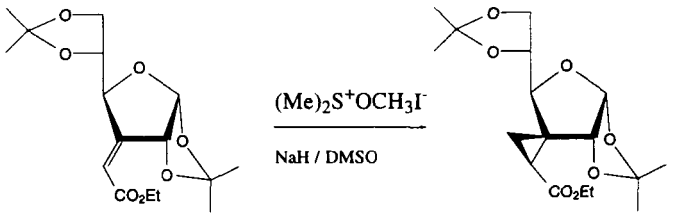
Treatment of **4** with $CH_2N_2/Pd(OAc)_2$ in ether at -40 °C gave one major and one minor product.[9] The minor product (20%) was identical with **5** according to ^1H NMR and optical rotation data. The major product (80%) was (*Z*)-3-deoxy-3-*C*-[(methyl)-methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose **6**. In its ^1H NMR spectrum, the characteristic resonances due to vinylic methyl and vinylic proton were observed at 1.86 and 5.96 ppm, respectively (Scheme 2). The *Z*-geometry of the side chain was confirmed by NOE experiments.



4 **5** **6**

Scheme 2

In an alternative strategy, the cyclopropanation of **3** was effected with dimethylsulfur ylide[10] obtained from $(Me)_2S^+OCH_3I^-$/NaH in DMSO. This reaction produced **7** as a single product in 85% yield (Scheme 3). The structure of compound **7** was proved by later reactions (Scheme 6).

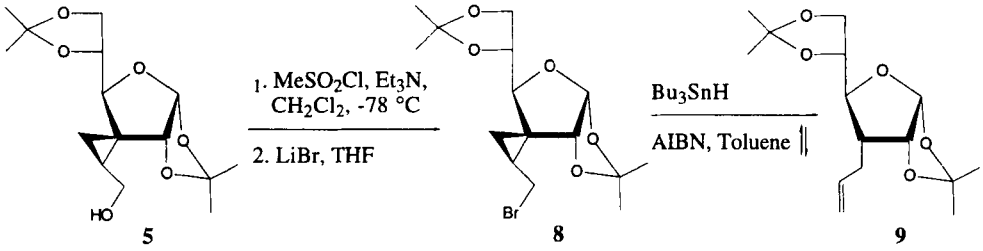


3 **7**

Scheme 3

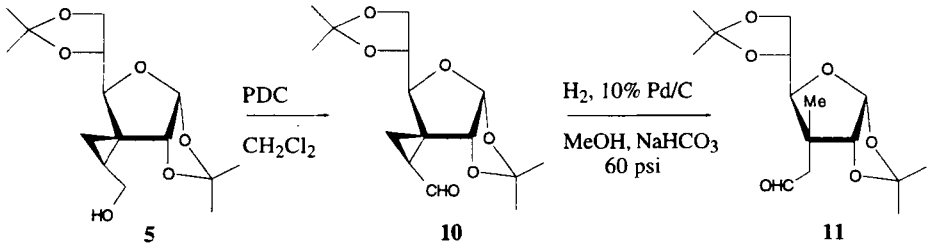
Our next concern involved conversion of **5** into the target molecule **1**. For this endeavour, a radical induced ring opening reaction was investigated. Thus, compound **5** was treated with $MeSO_2Cl/Et_3N$ in CH_2Cl_2 at -78 °C to afford the mesylate which was treated with LiBr in THF to give the bromide **8**. Subsequent treatment of **8** with Bu_3SnH/AIBN under reflux in toluene gave 3-*C*-allyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **9** in 76% yield. In the ^1H NMR spectrum of **9**, the characteristic signals of the allyl group were distinctly visible. In addition, the triplet at 4.58 ppm (J = 4.0 Hz) assigned to H-2 clearly indicated that the allyl group was present in an *allo*

configuration. From this sequence, it was apparent that a radical induced cyclopropane ring opening reaction occurred in an undesired mode (Scheme 4).



Scheme 4

In order to activate the cyclopropane ring in **5**, it was oxidised with PDC in CH_2Cl_2 to afford the rather unstable aldehyde **10** in 90% yield. Subsequent hydrogenation of **10** in the presence of 10% Pd/C at 60 psi, containing a catalytic amount of $NaHCO_3$, provided the aldehyde **11**. Based on NOE-studies as indicated in figure 2 the configuration at C-3 was assigned as shown (Scheme 5).



Scheme 5

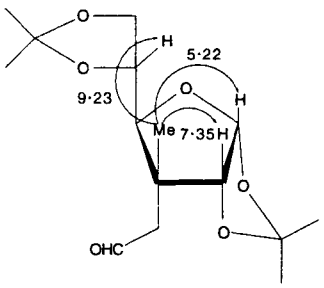
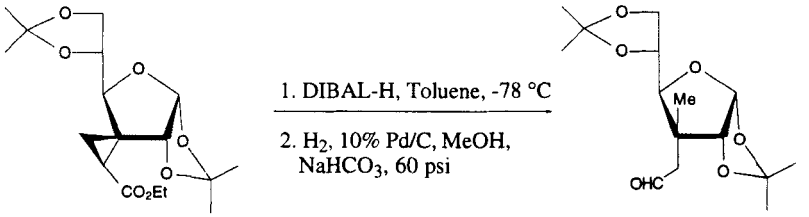


Figure 2. NOE study of compound **11**

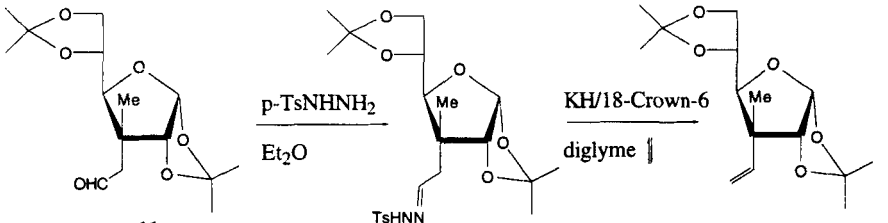
Previously synthesised compound **7** was also transformed into **11** by a two step sequence involving DIBAL-H reduction and catalytic hydrogenation. This clearly proved the stereostructure of the parent cyclopropane derivative **7** (Scheme 6).



7 11

Scheme 6

Conversion of **11** into the *C*-vinyl derivative **1** was effected by the Bamford-Stevens reaction.[11] Accordingly, **11** was treated with *p*-tosylhydrazine in ether at room temperature to give the corresponding hydrazone derivative **12**. This was heated under reflux with KH/18-Crown-6 in diglyme for 3 h to afford the requisite product **1** in 60% yield. The spectral and optical rotation data of **1** were in full agreement with reported values (Scheme 7).[3c,d]



11 12 1

Scheme 7

CONCLUSION

In conclusion, new syntheses of 3,3-spirocyclopropane derivatives of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose were developed. One synthetic procedure was used to prepare the versatile natural product synthon (**1**) with a quaternary chiral centre.

EXPERIMENTAL

General methods. Optical rotations were measured on JASCO DIP-370 digital polarimeter at 22 °C. NMR spectra were recorded on Varian Gemini 200 MHz in $CDCl_3$. Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were recorded on VG microMass 7070H (LRMS) and VG AutoSpec M (HRMS) spectrometers. Silica gel (60-120 mesh, Acme, India) was used for column chromatography.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-(3*S*)-3,3-*C*-[(*S*)-(hydroxymethyl)ethylene]-α-D-*ribo*-hexofuranose (5).

$Pd(OAc)_2$-CH_2N_2 method. To a mixture of **4** (2.0 g, 6.99 mmol) and CH_2N_2 (prepared from 19.0 g of *N*-methylnitroso urea and KOH) in ether (25 mL) at -40 °C was added $Pd(OAc)_2$ (78 mg). The reaction mixture was stirred for 1 h, concentrated and then purified on silica gel by using ethyl acetate-light petroleum (1:9) to give (*Z*)-3-deoxy-3-*C*-[(methyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose **6** as a syrup (1.51 g, 80%): $[\alpha]_D$ 105.4° (*c* 1.42, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35,1.38,1.42,1.48 (4s, 12 H, 2 x Me_2C), 1.86 (dd, 3 H, J = 2.0 Hz, 8.0 Hz, C=CH*Me*), 3.87-4.06 (m, 3 H, H-5, H-6a and H-6b), 4.52 (m, 1 H, H-4), 5.08 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-2), 5.76 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 5.96 (m, 1 H, C=C*H*-Me). Further elution with ethyl acetate-light petroleum (1:3) to give **5** as a syrup (0.38 gm, 20%): $[\alpha]_D$ 46° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.50 (t, 1H, J = 6.2 Hz, one of cyclopropane CH_2), 1.25 (t, 1H, J = 6.2 Hz, one of cyclopropane CH_2), 1.27, 1.33, 1.38, 1.59 (4s, 12H, 2 x Me_2C), 1.66 (m, 1H, cyclopropane C*H*), 2.93 (brs, 1H, OH), 3.23 (t, 1H, J = 10.4 Hz, one of CH_2OH), 3.70 (m, 1H, H-5), 3.85 - 4.20 (m, 4H, H-4, H-6a, H-6b one of CH_2OH), 4.40 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-2), 5.82 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1). HRMS Calcd for $C_{14}H_{21}O_6$; 285.1338 $[M-Me]^+$. Found : 285.1339 (error 0.3 ppm).

Simmons-Smith method. 1M solution of diethylzinc (14 mL, 13.98 mmol) and CH_2I_2 (2.25 mL, 27.97 mmol) in CH_2Cl_2 (25 mL) at -40 °C were stirred for 0.5 h. Compound **4** (2.0 g, 6.99 mmol) in CH_2Cl_2 (25 mL) was slowly added. After 3 h, the reaction mixture was quenched by adding water and the organic layer separated, dried and concentrated. The residue was purified by column chromatography on silica gel by eluting with ethyl acetate-light petroleum (1:3) to give compound **5** as a syrup (1.52 g, 80%).

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-(3*S*)-3,3-*C*-[(*S*)-(ethoxycarbonyl)ethylene]-α-D-*ribo*-hexofuranose (7). A solution of NaH (60% dispersion in oil, 92 mg, 2.30 mmol) in dry DMSO (5 mL) was cooled to 0 °C and then trimethylsulfoxonium iodide (0.50 g, 2.30 mmol) was added. After 15 min, compound **3** (0.50 g, 1.52 mmol) in DMSO (2 mL) was introduced. The reaction was stirred for 1 h, quenched with water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to give **7** as a syrup (0.44 g, 85%): $[\alpha]_D$ 155° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 - 1.50 (m, 17H, 2 x Me_2C, $COOCH_2Me$ and cyclopropane CH_2), 2.05 (dd, 1H, J = 6.66 Hz, 8.85 Hz, cyclopropane C*H*), 3.64 (m,

1H, H-5), 3.83 (dd, 1H, $J_{5,6a}$ = 5.55 Hz, $J_{6a,6b}$ = 8.88 Hz, H-6a), 3.97-4.15 (m, 4H, COOCH_2Me, H-4 and H-6b), 4.49 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-2), 5.70 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1). HRMS Calcd for $C_{16}H_{23}O_7$; 327.1443 (M-Me)+. Found: 327.1449 (error 1.7 ppm).

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-allyl-α-D-allofuranose (9). A solution of **5** (1.5 g, 5.00 mmol), Et_3N (14 mL, 10.00 mmol) in CH_2Cl_2 (25 mL) was cooled to -78 °C and then MsCl (0.69 mL, 8.55 mmol) was added. After 45 min. LiBr (0.80 g, 10.00 mmol) in THF (15 mL) was introduced. The colourless mixture was warmed slowly to -20 °C and stirred for 1 h. Then the mixture was poured over water and extracted with CH_2Cl_2, washed with water, dried and concentrated. The residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to give **8** (1.75 g, 84%).

A solution of compound **8** (0.75 g, 2.07 mmol), Bu_3SnH (0,68 mL, 2.48 mmol) and AIBN (18 mg) in toluene (20 mL) was refluxed for 3 h and concentrated. The residue was dissolved in ethyl acetate, washed with water, dried and concentrated. The residue was purified on silica gel by using ethyl acetate-light petroleum (1:9) as eluent to give compound **9** as a syrup (0.45 g, 76%): $[\alpha]_D$ 30.7° (*c* 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32, 1.34, 1.38, 1.50 (4s, 12H, 2 x Me_2C), 1.85 (m, 1H, H-3), 2.24-2.48 (m, 2H, CH_2-CH=CH_2), 3.68 (m, 1H, H-5), 3.85-4.12 (m, 3H, H-4, H-6a and H-6b), 4.58 (t, 1H, $J_{1,2}$ = 4.0 Hz, H-2), 5.00 (d, 1H, J = 10.0 Hz, one of CH_2-CH=CH_2), 5.10 (d, 1H, J = 16.0 Hz, one of CH_2-CH=CH_2), 5.68 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.85 (m, 1H, CH_2-C*H*=CH_2). HRMS Calcd for $C_{14}H_{21}O_5$; 269.1388 (M-Me)+. Found: 269.1378 (error 3.8 ppm).

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-(3*S*)-3,3-*C*-[(*S*)-(formyl)-ethylene]-α-D-*ribo*-hexofuranose (10).

By oxidation of 5. A solution of compound **5** (1.5 g, 5.00 mmol), PDC (2.25 g, 6.00 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 1 h. The reaction mixture was poured over a dry silica gel column and eluted with ether to give the aldehyde **10** (1.3 g, 90%).

By reduction of 7. To a solution of compound **7** (0.50 g, 1.46 mmol) in dry toluene (15 mL) at -78 °C, DIBAL-H (6 mL of 2.5N, 1.46 mmol) was added. The reaction mixture was stirred for 2 h, quenched by adding sodium potassium tartrate and warmed to room temperature. The organic layer was separated and washed with water, dried and concentrated. The residue was purified on silica gel by eluting with ethyl acetate - light petroleum (1:9) to give compound **10** as a syrup (0.43 g, 90%): $[\alpha]_D$ 60.5° (*c* 1.1,

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (s, 6H, Me_2C), 1.38 (s, 3H, one of Me_2C), 1.50 (t, 1H, J = 5.4 Hz, one of cyclopropane CH_2), 1.51 (s, 3H, one of Me_2C), 1.69 (dd, 1H, J = 5.4 Hz, one of cyclopropane CH_2), 2.37 (m, 1H, cyclopropane CH), 3.75 (m, 1H, H-5), 3.95 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 9.46 Hz, H-6a), 4.11 (m, 2H, H-4 and H-6b), 4.52 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-2), 5.81 (d, 1H, $J_{1,2}$ = 4.1 Hz, H-1), 9.39 (d, 1H, J = 5.4 Hz, CHO).

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-formamethyl-α-D-allofuranose (11). A solution of **10** (1.0 g, 3.35 mmol), 10% Pd-C (0.10 g) and $NaHCO_3$ (10 mg) in MeOH (20 mL) was stirred under H_2 at 60 psi for 6 h. The mixture was filtered through Celite, concentrated and purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to give **11** as a syrup (0.65 g, 65%): $[\alpha]_D$ 55.7° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.03, 1.21, 1.25, 1.32, 1.43 (5s, 15H, 2 x Me_2C and Me), 2.69 (s, 2H, CH_2CHO), 3.54 (dd, 1H, $J_{5,6a}$ = 8.8 Hz, $J_{5,6b}$ = 14.7 Hz, H-5), 3.78-4.08 (m, 3H, H-4, H-6a and H-6b), 4.48 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-2), 5.66 (d, 1H, $J_{1,2}$ = 3.2 Hz, H-1), 9.70 (s, 1H, CHO). Crude **10** was used directly for the preparation of **12**.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-3-*C*-vinyl-α-D-allofuranose (1). A solution of compound **11** (0.50 g, 1.66 mmol) and *p*-tosyl hydrazine (0.35 g, 1.66 mmol) in ether (10 mL) was stirred for 4 h at room temperature. Solvent was removed to give the hydrazone derivative **12** (0.73 g, 90%). Crude **12** was used without further purification for conversion to **1**.

To a suspension of KH [0.47 g of 20% dispersion in oil (11.68 mmol) in diglyme (10 mL)], hydrazone derivative **12** (0.73 g, 1.56 mmol) and 18-crown-6 (7 mg) were added followed by heating under reflux for 3 h. Diglyme was removed and the residue extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column using ethyl acetate-light petroleum (1:9) as eluent to give compound **1** as a syrup (0.28 g, 60%): $[\alpha]_D$ 63° (*c* 0.73, $CHCl_3$); [lit.[3c,d] $[\alpha]_D$ 67.5° (*c* 1.28, $CHCl_3$)]; HRMS Calcd for $C_{15}H_{24}O_5$; 284.1623 (M^+). Found: 284.1610 (error 4.8 ppm).

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