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Radical-mediated stereoselective synthesis of (+)-dihydrocanadensolide and (−)-3-*epi*-dihydrocanadensolide from D-xylose†

G. V. M. Sharma* and T. Gopinath

D-211, Discovery Laboratory, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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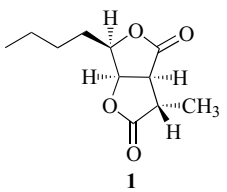
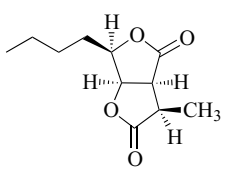
Abstract—An intramolecular radical cyclisation protocol on 5-hexenyl systems was utilised for the first time in a synthesis of (+)-dihydrocanadensolide and its C-3 epimer. This study also revealed the effect of the additional stereocentre at the 2′-position of the radical systems. © 2001 Elsevier Science Ltd. All rights reserved.

Regio- and stereoselective radical[1] cyclisation reactions play a crucial role for C–C bond formation, in particular for the synthesis of *cis*-fused bicyclic systems via efficient intramolecular routes. Such a protocol on templates derived from monosaccharides has attracted a lot of attention resulting in the synthesis of several bioactive compounds especially those containing bis-butyrolactone moieties. Earlier, by the adoption of an intramolecular route on 5-hexynyl systems, we reported the synthesis of avenaciolide[2] and canadensolide,[3,4] and the first synthesis and structure determination of sporothriolide,[5] 4-*epi*-ethisolide[5] and discosiolide.[6] In continuation of our studies on radical routes on sugar templates, herein, we describe the synthesis of (+)-dihydrocanadensolide and its C-3 epimer from D-xylose.

Dihydrocanadensolide **1** was isolated as a mold metabolite with biological activity from *Penicillium canadense*.[7,8] Its first total synthesis was reported by Mulzer,[9] while **1**[10] and its epimer **2**[11] were also synthesised. The main strategy of the present synthesis involves the utilisation of radical cyclisation of 5-hexenyl systems derived from D-xylose.



1



2

The regio- and stereochemical outcome of radical cyclisations on systems[12] with 2, 3, 4 and 5 stereocentres has been well studied and many reactions are well defined theoretically.[13,14] It is well known in the literature that the presence of a stereocentre at C-2 in a radical system generates a 1,2- and 1,5-*cis* fused bicyclic system as the only, or major, product. In this context, our interest was to see the impact of an additional stereocentre at the 2′-position, which would alter the ratios of the products (1,5-*cis*/*trans*) and could be exploited in synthetic studies on **1** and **2**. Unlike our earlier studies using 5-hexynyl systems, in the present study we were interested in observing the effect of the 2′-stereocentre (at the anomeric position) in addition to the stereocentre at the C-2 position of the radical carbon on the 5-hexenyl systems. The requisite, 2- and 2′-substituted radical systems were thus generated from D-xylose.

Accordingly, known diol **3**[15] (Scheme 1) was subjected to tosylation (TsCl, pyridine, CH_2Cl_2) to give **4**, which on subsequent reaction with *n*-propylmagnesium bromide afforded **5**. Reaction of **5** with allyl bromide (NaH, THF) gave **6**, $[\alpha]_D = -15.4$ [*c* 1.0, $CHCl_3$]. Further, hydrolysis of **6** (H^+ resin, MeOH) and treatment of the resultant alcohols **7**, (δ 4.94, d, $J = 7.0$ Hz, H-1) and **7a** (δ 4.68, d, $J = 2.3$ Hz, H-1) with NaH, CS_2 and MeI in THF furnished the xanthates **8** and **8a**, respectively, thus providing the radical precursors with 2- and 2′-stereocentres.

The xanthate **8** (Scheme 2) was subjected to cyclisation[16] with *n*-Bu_3SnH (AIBN, benzene, reflux) to afford a separable mixture of isomers **9** and **10** in a 3:1

* Corresponding author. E-mail: esmvee@iict.ap.nic.in

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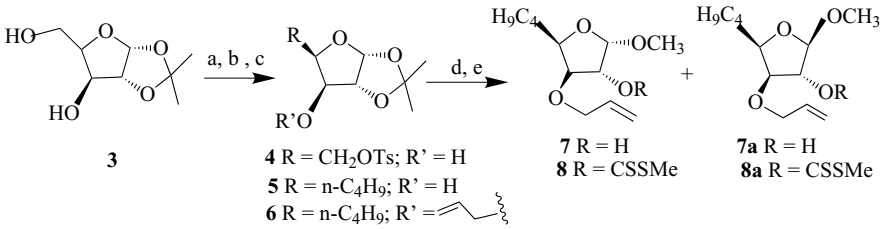
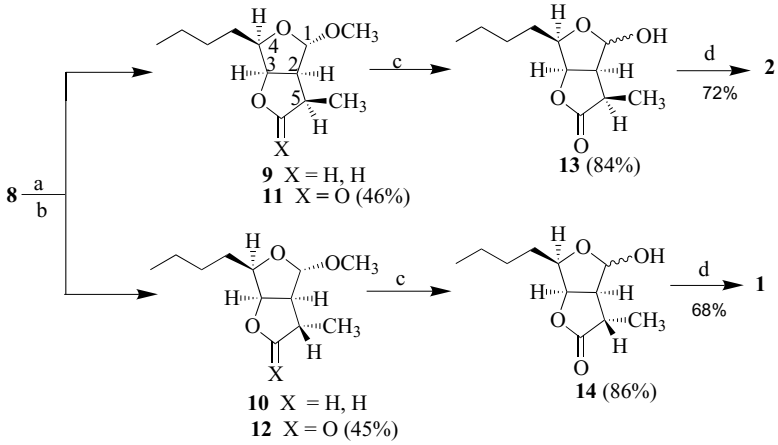


Scheme 1. *Reagents and conditions*: (a) TsCl, pyridine, CH_2Cl_2, rt, 6 h, 82%; (b) C_3H_7MgBr, dry THF, reflux, 10 h, 75%; (c) NaH, allyl bromide, dry THF, rt, 4 h, 83%; (d) MeOH, conc. HCl, reflux, 45 min, 91%; (e) NaH, CS_2, CH_3I, dry THF, 0°C to rt, 4 h, 78% (α), 81% (β).

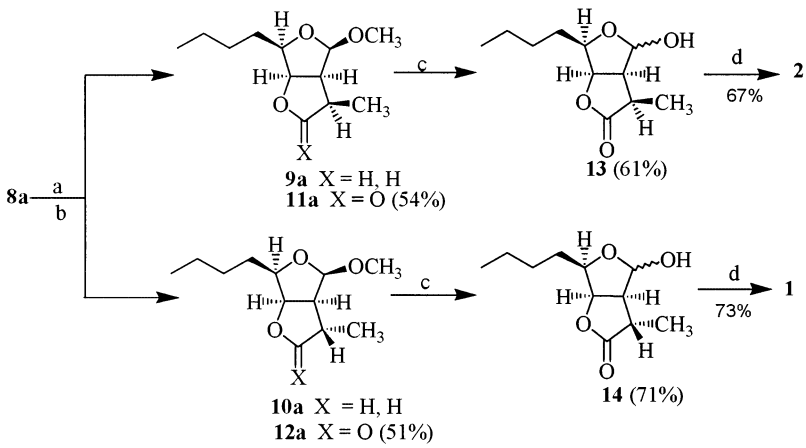


Scheme 2. *Reagents and conditions*: (a) *n*-Bu_3SnH, dry benzene, AIBN, reflux, 12 h, 82%; (b) CH_2Cl_2:CH_3CN:H_2O (2:2:3), $NaIO_4$, cat. $RuCl_3 \cdot H_2O$, rt, 18 h; (c) 60% CH_3COOH, 60°C, 30 min; (d) PDC, dry CH_2Cl_2, reflux, 2 h.

ratio, which on further oxidation with $RuCl_3$–$NaIO_4$[17] afforded the lactones **11** and **12**, respectively. The structures of these lactones were unambiguously assigned based on spectral analysis. Compound **11** was found to be 2,3- and 2,5-*cis*, while, **12** was 2,3-*cis* and 2,5-*trans*. On further hydrolysis (aq. AcOH-conc. HCl-cat.) lactones **11** and **12** furnished the lactols **13** and **14**, respectively. Finally, PDC oxidation of **13** and **14** in CH_2Cl_2 independently afforded **2** and **1**, respectively, whose optical rotation values and spectroscopic data were comparable with reported values.[10]

The study was next extended to see the effect of the β-anomeric stereocentre in **8a**. Accordingly, **8a** (Scheme 3) on cyclisation with *n*-Bu_3SnH, as described for **8**, gave **9a** and **10a** in a 1.5:1 ratio. This result amply indicated the effect of the 2′-stereocentre in **8** (α-OMe) and **8a** (β-OMe) on the cyclisation.

In a further study, **9a** and **10a** were converted into lactones **11a** and **12a**, respectively, with $RuCl_3$–$NaIO_4$ and subsequently transformed into the lactols **13** and **14**. Finally, oxidation of **13** and **14** resulted in the



Scheme 3. *Reagents and conditions*: (a) *n*-Bu_3SnH, dry benzene, AIBN, reflux, 12 h, 84%; (b) CH_2Cl_2:CH_3CN:H_2O (2:2:3), $NaIO_4$, cat. $RuCl_3 \cdot H_2O$, rt, 18 h; (c) 60% CH_3COOH, 60°C, 30 min; (d) PDC, dry CH_2Cl_2, reflux, 2 h.

formation of **2** and **1**, which were identical in all respects with the products prepared from the α-anomer **8**.

During the radical cyclisation of **8** and **8a**, the effect of the 2′-stereocentre in the xanthate in altering the ratios of the products **9** and **10** (3:1) **9a** and **10a** (1.5:1), may be explained as depicted in Fig. 1.

Compound **8** (R = OMe) undergoes cyclisation through 'chair-like' transition state 'A' to give the 2,5-*cis* product **9** (major) while the minor product **10** results through the transition state 'B'. Similarly, **8a** (R′ = OMe) gave **9a** through transition state 'A' while **10a** is formed through transition state 'B'. In the case of cyclisation of **8**, the 2,5-*cis* product **9** is the major product, where the α-OMe (C-1) and Me (C-5) are placed apart from each other. However, due to the presence of the β-OMe in **8a**, the cyclisation resulted in the prodcuts **9a** and **10a** in almost equal quantities (1.5:1). This change in the ratios of 2,5-*cis* to 2,5-*trans* products for the cyclisation of **8a**, may be attributed to the steric interaction between the β-OMe and the C-5 methyl group in **9a**, which is less pronounced in **10a**.

Thus, in the present study the first radical mediated route was developed for the synthesis of **1** and its C-3-epimer **2**. The formation of the 2,5-*trans* product and the change in the ratios of the products formed from the β-anomer, clearly indicate the effect of the 2′-stereocentre, which was well exploited for the successful synthesis of **1**.

Spectral analysis for selected compounds

Compound 11: $[\alpha]_D = +36.48$ (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 7.3$ Hz, CH_3), 1.20–1.50 (m, 7H, $2CH_2$, CH_3), 1.64–1.82 (m, 2H, CH_2), 2.86 (dq, 1H, $J = 9.8$, 7.0 Hz, H-5), 3.0 (dd, 1H, $J = 9.8$, 6.9 Hz, H-2), 3.32 (s, 3H, OMe), 4.02 (ddd, 1H, $J = 7.9$, 4.3, 3.6 Hz, H-4), 4.82 (dd, 1H, $J = 6.9$, 3.6 Hz, H-3), 4.96 (s, 1H, H-1); FABMS: 228 (M^+); IR (neat); 1770 cm^{-1}; **Compound 12**: $[\alpha]_D = +11.36$ (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 7.35$ Hz, CH_3), 1.16–1.50 (m, 7H, $2CH_2$, CH_3), 1.58–1.72 (m, 2H, CH_2), 2.50 (dq, 1H, $J = 9.1$, 6.8 Hz, H-5), 2.64 (dd, 1H, $J = 9.1$, 4.5 Hz, H-2), 3.30 (s, 3H, OMe), 3.94 (ddd, 1H, $J = 6.9$, 6.8, 4.5 Hz, H-4), 4.76 (s, 1H, H-1), 4.86 (dd, 1H, $J = 6.8$, 4.5 Hz, H-3); FABMS: 228 (M^+); IR (neat); 1770 cm^{-1}; **Compound 12a**: $[\alpha]_D = +13.96$ (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 7.4$ Hz, CH_3), 1.18–1.50 (m, 7H, $2CH_2$, CH_3), 1.58–1.76 (m, 2H, CH_2), 2.50 (dq, 1H, $J = 8.2$, 7.7 Hz, H-5), 2.65 (dd, 1H, $J = 8.2$, 4.5 Hz, H-2), 3.30 (s, 3H, OMe), 3.96 (ddd, 1H, $J = 6.9$, 5.9, 4.1 Hz, H-4), 4.77 (s, 1H, H-1), 4.89 (dd, 1H, $J = 6.9$, 4.5 Hz, H-3); FABMS: 228 (M^+); IR (neat); 1770 cm^{-1}; **Compound 11a**: $[\alpha]_D = +37.73$ (*c* 0.50, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 7.2$ Hz, CH_3), 1.22–1.54 (m, 7H, $2CH_2$, CH_3), 1.64–1.80 (m, 2H, CH_2), 2.84 (dq, 1H, $J = 8.9$, 7.3 Hz, H-5), 2.98 (dd, 1H, $J = 9.1$, 6.9 Hz, H-2), 3.32 (s, 3H, OMe), 3.98 (ddd, 1H, $J = 7.7$, 7.4, 3.2 Hz, H-4), 4.80 (dd, 1H, $J = 6.9$, 3.2 Hz, H-3), 4.94 (s, 1H, H-1); FABMS: 228 (M^+); IR (neat); 1770 cm^{-1}; **Compound 1**: mp 92°C; lit.[10] mp 94°C; $[\alpha]_D = +30.9$ (*c* 0.50, $CHCl_3$); lit.[10] $[\alpha]_D = +29.8$ (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, $J = 7.6$ Hz, CH_3), 1.38–1.55 (m, 7H, $2CH_2$, CH_3), 1.76–1.98 (m, 2H, CH_2), 3.02 (dq, 1H, $J = 8.0$, 1.2 Hz, H-5), 3.08 (dd, 1H, $J = 6.4$, 1.2 Hz, H-2), 4.50 (ddd, 1H, $J = 7.2$, 6.8, 4.4 Hz, H-4), 5.05 (dd, 1H, $J = 6.4$, 4.4 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 17.1, 22.4, 27.5, 28.5, 38.3, 49.0, 78.3, 82.4, 174.6, 176.7; FABMS: 213 (M^++1); IR ($CHCl_3$): 1770 cm^{-1}; **Compound 2**: mp 53°C; $[\alpha]_D = -18.02$ (*c* 0.75, $CHCl_3$); lit.[10] $[\alpha]_D = -20.2$ (*c* 0.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.2$ Hz, 3H, CH_3), 1.30–1.54 (m, 7H, $2CH_2$, CH_3), 1.74–1.94 (m, 2H, CH_2), 3.08 (dq, 1H, $J = 10.0$, 7.3 Hz, H-5), 3.45 (dd, 1H, $J = 10.0$, 6.0 Hz, H-2), 4.50 (ddd, 1H, $J = 7.2$, 6.8, 4.5 Hz, H-4), 5.02 (dd, 1H, $J = 6.0$, 4.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.9, 13.8, 22.4, 27.4, 28.4, 36.6, 44.6, 77.9, 81.6, 172.0, 176.2; FABMS: 213 (M^++1); IR ($CHCl_3$): 1770 cm^{-1}.

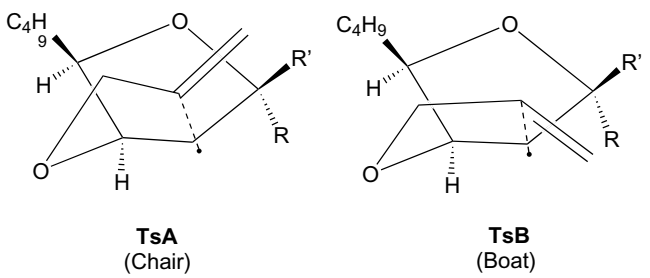


Figure 1.

Acknowledgements

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