Tetrahedron Letters, Vol.31, No.34, pp 4899-4902, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

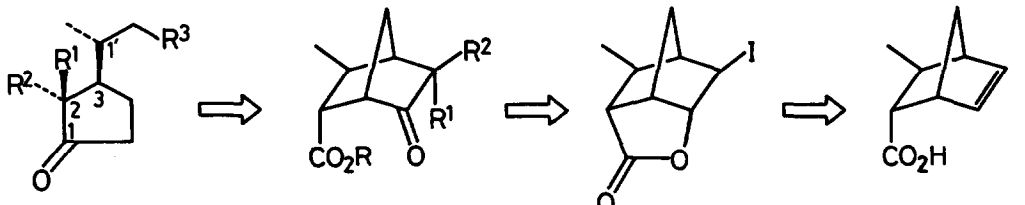
SYNTHESIS OF VITAMIN D_3 D RING SYNTHONS BY REDUCTIVE CLEAVAGE OF NORBORNAN-6-ONE-2-CARBOXYLATES

Isao Shimizu*, Naoto Matsuda, Yasuo Noguchi, Yoshiro Zako, and Kazuo Nagasawa

Department of Applied Chemistry, School of Science and Engineering,
Waseda University
Ookubo, 3-4-1, Shinjuku-ku, Tokyo 169, Japan

Summary: Reductive cleavage of 5-methylnorbornan-6-one-2-carboxylates with lithium metal in liquid ammonia gave 3-(1-methyl-2-methoxycarbonylethyl)cyclopentanones in good yields.

Cyclopentanoids **1** which have vicinal asymmetric carbon centers both in cyclopentane rings (C-3) and in their side chains (C-1') are ubiquitous in natural terpenoids and steroids.[1] So far several stereoselective methods have been reported for construction of these asymmetric centers.[2] In our synthetic study toward vitamin D_3s, we have developed a facile preparative method for 3-(1-methylalkyl)cyclopentanones. In this paper we wish to report a novel synthesis of VD_3 and 25-(OH)-VD_3 D ring synthons **(±)-1c** and **(-)-1d** by cleavage of a norbornane skeleton as shown in Scheme 1.

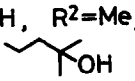


1 2 3 4

1a: $R^1=R^2=H$, $R^3=CO_2Me$

1b: $R^1=H$, $R^2=Me$, $R^3=CO_2Me$

1c: $R^1=Me$, $R^2=Allyl$, $R^3=CO_2Me$

1d: $R^1=H$, $R^2=Me$, $R^3=$ 

2a: $R^1=R^2=H$, $R=Me$

2b: $R^1,R^2=Me,H$, $R=Me$

2c: $R^1=Me$, $R^2=Allyl$, $R=Me$

2d: $R^1=R^2=R=H$

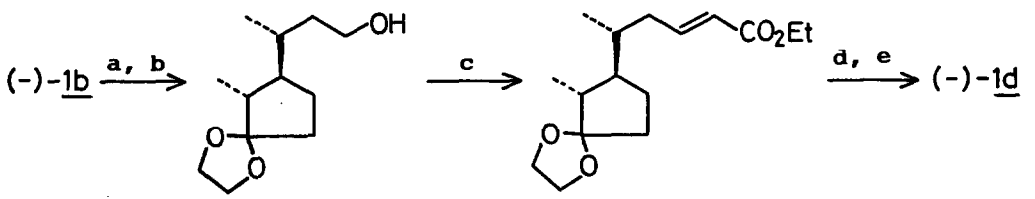
2e: $R^1,R^2=Me,H$, $R=H$

Scheme 1

The lactone **3**, which is readily accessible by iodolactonization of the Diels-Alder adduct **4**, was hydrolyzed with aqueous NaOH[3] to give the crude keto acid **2d** followed by esterification in refluxing methanol using a catalytic amount of p-TsOH to afford **2a** (61% yield from **4**). The keto ester **2a** dissolved in THF was added dropwise to a mixture containing excess lithium in liquid ammonia at -78°C and the mixture was stirred for 30 min. After addition of isoprene to destroy excess lithium, the resultant mixture was quenched with NH_4Cl. After usual work up and purification by chromatography on SiO_2 gave the cyclopentanone **1a** in 80% yield.[4,5]

Although regio- and stereoselective alkylation of **1a** at C-2 to afford **1b** or **1c** is difficult, **1b** and **1c** were easily obtained since alkylation was carried out selectively before the reductive cleavage, and the optically active cyclopentanone **(-)-1b** was prepared. Thus, reaction of the optically active acid **(+)-2d** ($[\alpha]^{23}_D$=+76.2°, c 1.10, $CHCl_3$) prepared as above from **(+)-4**[6] with 2.4 equivalent of LDA followed by quenching the dianion with MeI (4 eq) gave **(+)-2e**, which was esterified (MeOH, H^+) to afford the ester **(+)-2b**. Reductive cleavage of **(+)-2b** was carried out in a similar manner as described above to give **(-)-1b** ($[\alpha]^{25}_D$=-59.1°, c 1.4, $CHCl_3$) as a single stereoisomer by ^{13}C-NMR in 54% yield.

The chiral cyclopentanone **(-)-1b** was converted to the keto alcohol **(-)-1d** in 6 steps. Protection of the carbonyl group with ethylene glycol followed by reduction of the ester with $LiAlH_4$ gave the alcohol **(+)-5** ($[\alpha]^{24}_D$=+46.9°, c 1.2, $CHCl_3$). Oxidation of **(+)-5** with PCC followed by Emmons reaction afforded the ester **(+)-6**. Hydrogenation of **(+)-6** followed by reaction with methylmagnesium bromide and subsequent hydrolysis gave the alcohol **(-)-1d** ($[\alpha]^{24}_D$=-44.5°, c 1.2, $CHCl_3$), which is recognized as an intermediate of 25-(OH)-VD_3s.[2e,2i,7]

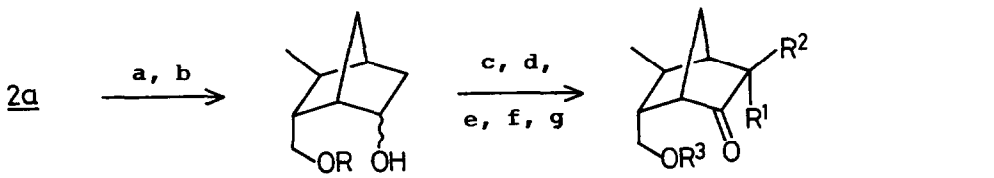


(+)-5 (+)-6

(a) $HO(CH_2)_2OH$, p-TsOH, PhH, reflux, 90%
(b) $LiAlH_4$, THF, 0°C, 89% **(c)** i PCC, Zeolite 3A, CH_2Cl_2,
ii $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 75% (2 Steps) **(d)** Pd/C, H_2, EtOAc, Et_3N, 95% **(e)** i MeMgBr, THF, 0°C, ii 3N-HCl, THF, 65% (2 steps)

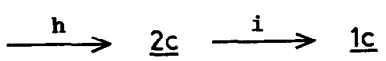
Scheme 2

Another steroid intermediate **1c** was also synthesized as a racemate stereoselectively from **2a**. The keto ester **2a** was reduced with $LiAlH_4$ followed by selective acetylation of the primary alcohol and Jones oxidation gave the acetoxy ketone **9**. After conversion of the acetyl group to silyl ether, the ketone **10** was methylated (LDA, MeI) to give **11** in 81% yield. Direct allylation of **11** to **12** using allyl bromide was unsuccessful. So we employed palladium-catalyzed decarboxylative allylation method.[8] Enolate formation from **11** followed by quenching with allyl chloroformate gave the β-keto ester **12** in 60% yield. Reaction of **12** with a catalytic amount of $Pd(OAc)_2$-PPh_3 in refluxing THF gave the allyl ketone **13**, which was converted to **2c** by Jones oxidation and esterification. Finally, reductive cleavage of **2c** afforded the cyclopentanone **1c** in 71% yield.[2j,9]



7 : R=H
8 : R=Ac

9 : $R^1=R^2=H$, $R^3=Ac$
10 : $R^1=R^2=H$, $R^3=TBDMS$
11 : R^1,$R^2=Me$,H , $R^3=TBDMS$
12 : R^1,$R^2=Me$, CO_2 ~, $R^3=TBDMS$
13 : $R^1=Me$, $R^2=Allyl$, $R^3=TBDMS$



(a) $LiAlH_4$, THF, 0°C, 83% **(b)** Ac_2O, py
(c) Jones oxidation, 56% (2 steps)
(d) **i** K_2CO_3, MeOH, **ii** TBDMS-Cl, imidazole, DMF, 95% (2 steps)
(e) LDA, MeI,THF, 81% **(f)** LDA, allyl chloroformate, THF, 60%
(g) $Pd(OAc)_2$, PPh_3, THF, reflux, 65% **(h)** **i** Jones oxidation, **ii** MeOH, p-TsOH, 70% (2 steps) **(i)** Li/NH_3, THF, -78°C, 71%

Scheme 3

Synthesis of chiral VD_3s from **(-)-1d** is in due course. This research was financially supported by Uehara Memorial Foundation.

References and Notes

1) Natural Products Chemistry; Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S., ed.; Kodansha Scientific: Tokyo, 1974, Vol. 1.

2) For recent works see, (a) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1987**, 92. (b) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1987**, 743. (c) Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311. (d) Takahashi, T.; Miyazawa, M.; Ueno, H.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 3881. (e) Hutchinson, J. H.; Money, T. *J. Chem. Soc., Chem. Commun.* **1986**, 288. (f) Taber, D. F.; Krewson, K. R.; Raman, K.; Rheingold, A. L. *Tetrahedron Lett.* **1984**, *25*, 5283. (g) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278. (h) Hatakeyama, S.; Numata, H.; Takano, S. *Tetrahedron Lett.* **1984**, *25*, 3617. (i) Desmaile, D.; Ficini, J.; Guingant, A.; Touzin, A. M. *Tetrahedron Lett.* **1983**, *24*, 3079, 3083. (j) Ziegler, F. E.; Mencel, J. J. *Tetrahedron Lett.* **1983**, *24*, 1859.

3) Beckmann, S.; Geiger, H.; Schaber-Kiechle, M. *Chem. Ber.* **1959**, *92*, 2419.

4) (a) Grimshaw, J.; Haslett, R. J. *J. Chem. Soc., Chem. Commun.* **1974**, 174. (b) Gassman, P. G.; Creary, X. *J. Chem. Soc., Chem. Commun.* **1972**, 1214.

5) **1a** : IR (neat) 1780, 1730 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.50-1.20 (m, 8H), 0.99 (d, J=7 Hz, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 218.16(s), 173.01 (s), 51.46 (s), 42.94 (t), 42.68 (d), 39.46 (t), 38.95 (t), 35.40 (d), 27.64 (t), 18.17 (q); HRMS $C_9H_{13}O_2$, m/z 153.0926 (-MeO); LRMS m/z 185.

6) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

7) **1d** : IR (neat) 3456, 1738 cm^{-1}; ^{1}H-NMR (60 MHz, CCl_4) δ 1.15 (s, 6H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 221.08, 70.304, 49.925, 46.558, 43.851, 36.972, 34.521, 32.728, 28.960, 23.142, 21.931, 17.471, 13.922; See reference 2i).

8) (a) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.

9) **1c** : ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-4.80 (m, 3H), 3.69 (s, 3H), 2.61-1.25 (m, 10H), 0.97 (s, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 222.78 (s), 173.54 (s), 134.38 (d), 118.52 (t), 52.18 (s), 51.57 (q), 46.12 (d), 42.02 (t), 39.89 (t), 37.68 (t), 32.14 (d), 23.88 (t), 19.37 (q), 17.92 (q); HRMS $C_{14}H_{22}O_3$, m/z 238.1591.

(Received in Japan 11 June 1990)