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A short synthesis of the carbocyclic core of Entecavir from Corey lactone

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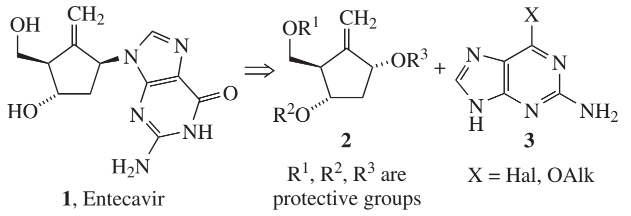
The readily available Corey lactone was converted in three simple stages to tris-TBS-ether of (1*R,3*R**,5*S**)-1-hydroxymethyl-3,5-dihydroxy-2-methylidenecyclopentane – the protected carbocyclic core of Entecavir, one of the best medicines against hepatitis.**

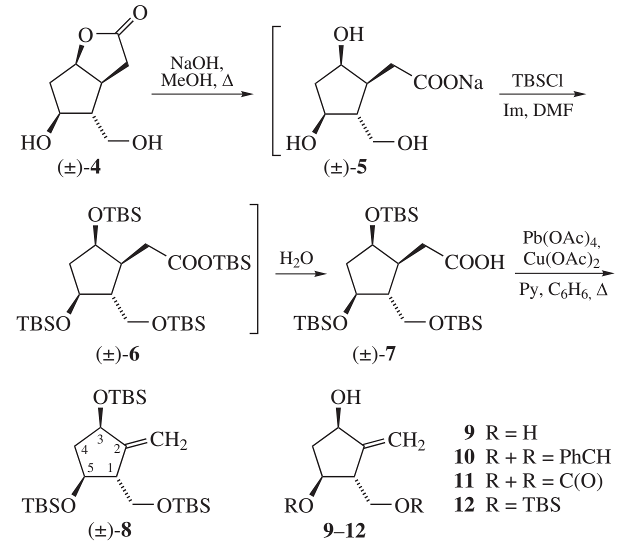
Of the medicines used in the treatment of hepatitis B, formulations based on carbanucleosides are currently deemed to be in greatest demand. Entecavir **1** developed and produced by Bristol–Myers–Squibb under trade name Baraclude[1,2] is the most important of these. It possesses high efficiency and selectivity to hepatitis B virus (ED_{50} = 3 nM),[3] does not show noticeable side effects and is convenient in use. A number of Entecavir syntheses were suggested, both from cyclopentane derivatives[4] and acyclic compounds.[5] An extensive review on this topic including patent data has been published by Slovak[6(a)] and Russian authors.[6(b)]

The main problems in Entecavir synthesis are related to the preparation of key cyclopentane intermediates. In particular, they include methylidenecyclopentanes with general formula **2** (Scheme 1). The final stage of the synthesis involves 'linking' carbocyclic moieties **2** with guanine derivatives **3** by the Mitsunobu reaction.



Scheme 1

The Corey lactone **4**,[7] a widely known prostaglandin synthon, is commercially available in racemic and both enantiomeric forms. Of the four substituents at the cyclopentane ring in the (+)-Corey lactone molecule, three ones are the same as those in type **2** compounds, both in chemical nature and in mutual arrangement and relative configuration. Here we have shown for racemic Corey lactone (±)-**4**[7(c)] as an example that the Corey lactone can be easily converted by transformation of the fourth substituent into compound **8** of type **2**, which is a new carbocyclic synthon for Entecavir (Scheme 2).



Scheme 2

Exhaustive silylation of the Na salt of trihydroxy acid **5**, which was obtained by alkaline hydrolysis of lactone **4**, gave tetra-TBS derivative **6**. The most labile carboxyl TBS group was removed from the latter by water treatment without isolation. This three-stage one-pot transformation afforded acid **7** in 70% yield.[†] Surprisingly, oxidative decarboxylation of acid **7** with the $Pb(OAc)_4/Cu(OAc)_2$ system[8] occurred smoothly to give methylidenecyclopentane **8** in 78% yield.[‡] Attempts to use cheap Me_3SiCl or Et_3SiCl in this scheme instead of the expensive TBSCl

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[†] IR spectra were recorded in a film or in Nujol using a Shimadzu IR Prestige-21 spectrophotometer. NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) in $CDCl_3$. Signals of $CDCl_3$ (δ_H 7.27, δ_C 77.00) were used as internal standards. The mass spectrum was obtained using a ThermoFinnigan MAT 95XP instrument; the ionization energy was 70 eV. The progress of the reactions was monitored by 'Sorbfil' TLC method. The final reaction mixtures were extracted with EtOAc. The extract was washed with brine and dried with Na_2SO_4, then evaporated and chromatographed on silica gel.

(1S,2R*,3S*,5R*)-3,5-Bis[*tert*-butyl(dimethyl)silyloxy]-2-{[*tert*-butyl-(dimethyl)silyloxy]methyl}cyclopentylacetic acid* **7**. A solution of lactone **4** (280 mg, 1.62 mmol) and NaOH (130 mg, 3.25 mmol) in dry methanol (6 ml) was refluxed for 2 h. The solution was then evaporated and the residue was dried for 3 h *in vacuo* (25 °C/2 Torr). The resulting powdery residue was dissolved in dry DMF (3 ml). Imidazole (880 mg, 13.0 mmol) and TBSCl (1.47 g, 9.7 mmol) were added to the solution and the mixture was stirred for 12 h at 25 °C. Water (15 ml) was then added and the reaction mixture was stirred for 4 h until complete conversion of ester **6** to acid **7**. Treatment gave 610 mg (70%) of compound **7**, oil, R_f 0.6 (light petroleum–ethyl acetate, 7:3). IR (ν/cm^{-1}): 3200–2400, 1702, 1463, 1251, 1122, 837, 775. ^{1}H NMR ($CDCl_3$) δ: 0.057, 0.065, 0.067, 0.098 and 0.10 (5 s, 18 H, 6 MeSi), 0.78 and 0.80 (2 s, 27 H, 3 Bu^t), 1.55 (ddd, 1H, H^{4A}, *J* 4.4, 6.6, 11.0 Hz), 1.80 (m, 1H, H^1), 2.10–2.25 (m, 2 H, H^{4B}, H^2), 2.45 (dd, 1H, C*H*^{A}COOH, *J* 4.2, 16.7 Hz), 2.65 (dd, 1H, C*H*^{B}COOH, *J* 9.6, 16.7 Hz), 3.62 (dd, 1H, C*H*^{A}OTBS, *J* 2.9, 10.3 Hz), 3.68 (dd, 1H, C*H*^{B}OTBS, *J* 3.8, 10.3 Hz) 3.95 (quint, 1H, H^3, *J* 7.7 Hz), 4.20 (quint, 1H, H^5, *J* 6.6 Hz), 10.05 (br. s, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: –5.56, –4.48 and –4.52 (all MeSi), 17.97 and 18.21 (all CSi), 25.82 and 25.87 (both Me), 32.80 (*C*H$_2$COOH), 40.20 (C^1), 44.28 (C^4), 52.68 (C^2), 60.94 (CH_2OSi), 71.67 (C^3 and C^5), 179.30 (COOH). Found (%): C, 58.62; H, 10.44. Calc. for $C_{26}H_{56}O_5Si_3$ (%): C, 58.59; H, 10.59.

failed, since considerable reverse lactonization was observed during preparation of compounds **6** and **7**.

The use of 1′,3,5-tris-ether **8** in the synthesis of Entecavir requires derivatives with a free 3-hydroxy group. The required differentiation of oxygen functions can be achieved by selective protection of the 1′,5-diol moiety in diol **9** that is easy to obtain from triether **8** (see Scheme 2), *e.g.*, in the form of benzylidene-acetal **10**[9] or carbonate **11**, as well as by selective desilylation of allylic 3-OTBS group to produce the well known synthon **12**.[5(*a*)] Obviously, the use of (+)-Corey lactone should bring about enantiomerically pure synthon **8** with absolute configuration matching that of Entecavir.

Thus, we have developed an easy short synthesis of a new carbocyclic core of Entecavir from the Corey lactone in a total yield above 50%.

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References

1 G. S. Bisacchi, S. T. Chao, C. Bachard, J. P. Daris, S. F. Innaimo, G. A. Jacobs, O. Kocy, P. Lapointe, A. Martel, Z. Merchant, W. A. Slusarchyk, J. E. Sundeen, M. G. Yong, R. Colonno and R. Zahler, *Bioreg. Med. Chem. Lett.*, 1997, **7**, 127.

2 S. F. Innaimo, M. Seifer, G. S. Bisacchi, D. N. Strandring, R. Zahler and R. J. Colonno, *J. Antimicrob. Agents Chemother.*, 1997, **41**, 1444.

3 E. Ruediger, A. Martel, N. Meanwell, C. Solomon and B. Turmel, *Tetrahedron Lett.*, 2004, **45**, 739.

4 F. E. Ziegler and M. A. Sarpong, *Tetrahedron*, 2003, **59**, 9013.

5 (*a*) B. Zhou and Y. Li, *Tetrahedron Lett.*, 2012, **53**, 502; (*b*) X. Liu, X. Jiao, Q. Wu, Ch. Tian, R. Li and P. Xie, *Tetrahedron Lett.*, 2012, **53**, 3805; (*c*) J. Velasco, X. Ariza, L. Badia, M. Barta, R. Bereguluer, J. Farràs, J. Gallardo, J. Garcia and Y. Gasanz, *J. Org. Chem.*, 2013, **78**, 5482.

6 (*a*) M. Campian, M. Putala and R. Sebesta, *Curr. Org. Chem.*, 2014, **18**, 2808; (*b*) E. S. Matyugina, A. P. Khandazhinskaya and S. N. Kochetkov, *Russ. Chem. Rev.*, 2012, **81**, 729.

7 (*a*) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu and T. K. Schaaf, *J. Am. Chem. Soc.*, 1971, **93**, 1490; (*b*) I. Tömösközi, L. Gruber, J. Kovács, I. Székely and V. Simonidesz, *Tetrahedron Lett.*, 1976, **50**, 4639; (*c*) G. A. Tolstikov, M. S. Miftakhov, F. A. Valeev, N. S. Vostrikov and R. R. Akhmetvaleev, *Zh. Org. Khim.*, 1984, **20**, 1672 (in Russian).

8 J. H. Rigby, A. Payen and N. Warshakoon, *Tetrahedron Lett.*, 2001, **42**, 2047.

9 D. Alberico, J. Clayton, C. Dixon and B. Gorin, *WIPO patent WO 2011/150512 A1*, 2011.

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[‡] *(1*R**,3*R**,5*S**)-3,5-Bis[*tert*-butyl(dimethyl)silyloxy]-1-[*tert*-butyl(dimethyl)silyloxymethyl]-2-methylidenecyclopentane* **8**. Cu(OAc)$_2$ (8 mg, 0.044 mmol) was added to a solution of acid **7** (95 mg, 0.178 mmol) and pyridine (53 μl, 0.65 mmol) in dry benzene (6 ml). The mixture was stirred for 30 min at 25 °C, then Pb(OAc)$_4$ (470 mg, 1.1 mmol) was added and the mixture was refluxed for 1 h (TLC). Treatment gave 50 mg (78%) of compound **8** and 20 mg (21%) of unreacted acid **7**. Compound **8**, colorless oil, R_f 0.33 (light petroleum–ethyl acetate, 100:1). IR (ν/cm^{-1}): 1472, 1360, 1256, 1094, 836, 775. ^{1}H NMR (CDCl$_3$) δ: 0.0053, 0.027, 0.048, 0.07 and 0.087 (5 s, 15 H, 6 MeSi), 0.87 and 0.96 (2 s, 27 H, 3 Bu^t), 1.59 (dt, 1H, H^{4A}, J 1.3, 9.7, 11.3 Hz), 2.20 (dt, 1H, H^{4B}, J 4.9, 6.6, 11.3 Hz), 2.45 (m, 1H, H^1), 3.68 (dd, 1H, C$H^{1'A}$OTBS, J 3.3, 9.7 Hz), 3.72 (dd, 1H, C$H^{1'B}$OTBS, J 4.1, 9.7 Hz), 4.06 (dt, 1H, H^3, J 3.2, 6.6, 9.7 Hz), 4.30 (m, 1H, H^5), 4.90 (br. s, 1H, C=CH^A), 5.10 (m, 1H, C=CH^B). ^{13}C NMR (CDCl$_3$) δ: –4.79, –4.50 and –4.45 (all MeSi), 17.99 and 18.26 (both CSi), 25.81 (Me), 44.17 (C^4), 53.53 (C^1), 63.22 (CH$_2$OSi), 69.18 (C^5), 72.89 (C^3), 106.53 (=CH$_2$), 153.90 (C^2). MS, *m*/*z*: 485.3303 [M–H]$^+$. (calc. for C$_{25}$H$_{54}$O$_3$Si$_3$, *m*/*z*: 485.3297).