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The Synthesis of (4R-cis)-1,1-Dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate, a Key Intermediate for the Preparation of CI-981, a Highly Potent, Tissue Selective Inhibitor of HMG-CoA Reductase

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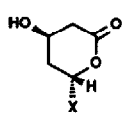
Abstract: *Three alternative methods for the synthesis of the optically active heptanoate (**6**), a key intermediate in the preparation of a highly potent and tissue selective HMG Co-A reductase inhibitor are described.*

Inhibitors of HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis, are receiving considerable attention due to their proven efficacy at lowering both total plasma and low density lipoprotein cholesterol in man.[1] This is evidenced by the significant number of recent reports on both natural[2] and synthetic[3] inhibitors. In particular, several different approaches to the key structural feature, the β-hydroxy-δ-lactone (**1**) or its open chain analogue (**2**), have been reported.[3,4]



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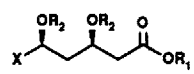
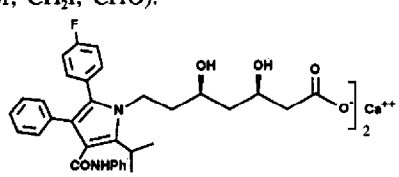
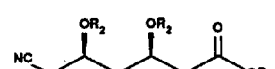


2

An important aspect of these previous syntheses is that they all provide a functional group "X" suitable for carbon-carbon bond formation to the "bulky lipophilic" portion of these compounds (i.e. X = CH_2OH, CH_2Br, CH_2I, CHO).



CI-981



3

CI-981, a potent and liver selective[5] member of the HMG-CoA reductase inhibitor class of compounds currently undergoing clinical trials, differs from most of these compounds in that the δ-lactone moiety is attached to a heteroaromatic group via the hetero-atom.[6] The original chiral synthesis of this compound employed the chiral acetate enolate chemistry developed by Braun.[3h,7] Unfortunately, due to the linear nature of this route, the overall yield was low. Thus, an alternative more economical route was sought.

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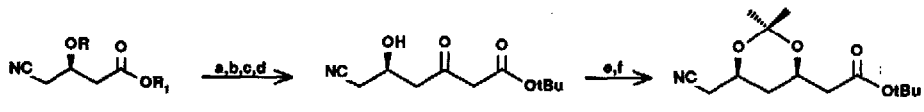
The retrosynthetic analysis we selected led to a δ-lactone moiety (**1**; X = CH_2CN) or the open chain analogue (**3**), as a key intermediate in the preparation of CI-981.

We herein report three efficient methods which have been applied in our laboratories for the synthesis of enantiomerically pure (4R-cis)-1,1-dimethylethyl 6-cyanomethyl-2,2-dimethyl-1,3-dioxane-4-acetate (**6**), the key intermediate in the synthesis of CI-981. Our initial approach to this intermediate centered on homologation of the 5 carbon subunit (**4**).[8,9]



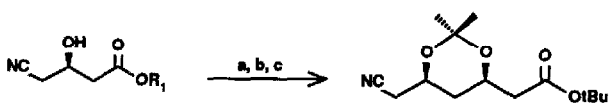
4 **5** **6**

R_1=Me, Et, n-Bu
R=TBDMS

a. NaOH; b. CDI; c. $Mg(O_2CCH_2CO_2tBu)_2$ d. Bu_4NF, AcOH, THF; e. $NaBH_4$, MeOH, $B(Et)_2OMe$, -90°C;
f. $(Me)_2C(OMe)_2$, $MeSO_3H$ gives 6 (60-65%).

The TBDMS protected compound **4** was hydrolyzed and chain extended by activation using N,N-carbonyldiimidazole followed by reaction with the magnesium salt of potassium t-butyl malonate.[10] Acidification followed by deprotection using buffered fluoride ion gave **5**.[11] Diastereoselective reduction using the procedure of Chen et al[12b,c] followed by protection as the acetonide resulted in **6**.[13] Overall, the yield of this sequence was 60-65%, with diastereoselectivity in the range of 100:1 (3R,5R:3S,5R). Recrystallization increases this ratio to ≈350:1 providing **6** with an enantiomeric purity of ≥99.5%.[14]

Alternatively a cross Claisen approach using lithium tert-butyl acetate and the unprotected compounds **7**[15] offered a shorter and more economical synthesis of **6**. While the cross Claisen has been used for the preparation of compounds of type **2**[4b,4c], the presence of the nitrile in the case reported here, provided an alternative site of reaction which could potentially cause difficulty. In practice, treatment of **7** with 3-4 eq. of lithium tert-butyl acetate resulted in smooth conversion to **5**, with no detectable reaction at the nitrile, in 75 to 80% yield. Conversion of **7** to **6** was achieved in 65 to 70% overall yield.



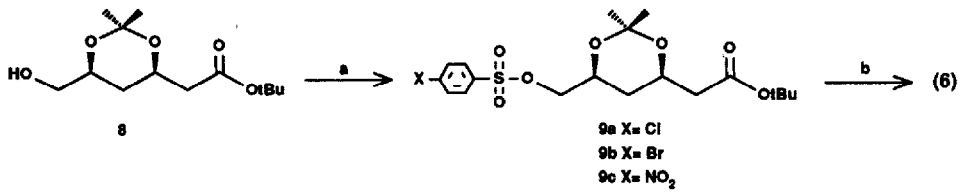
7 **6**

R_1=Me, Et, n-Bu

a. t-BuO_2CCH_3,LDA, Hexane,THF; then 7 in THF; b. $NaBH_4$, MeOH, $B(Et)_2OMe$,-90°C;
c. $(Me)_2C(OMe)_2$, $MeSO_3H$ gives 6 (65-70%).

The commercially available alcohol (**8**),[16] provided the starting point for the third route. It was envisioned that the primary hydroxyl group would be converted to a leaving group such as sulfonate (**9**) which would then be displaced by treatment with cyanide ion to provide the desired target (**6**). However, literature precedent[17] on an analogous compound indicated that a leaving group such as methanesulfonyl or toluenesulfonyl would be ineffective. Indeed, use of mesylate or tosylate provided clean reaction, in contrast to the earlier report[17], but require weeks to achieve significant conversions.

Use of the more activated nitro-or halo-substituted benzenesulfonates (**9**) provided significantly greater rates of reaction.[18] However, all were very sensitive to traces of moisture or acid and decomposed very rapidly on standing. The displacement reaction was sensitive to the stoichiometry of the cyanide and temperature.[19] With carefully controlled conditions the conversion of **8** to **6** was carried out in 85 to 90% overall yield. The final choice of activated sulfonyl ester was governed by cost of reagents, reaction rate, and yield. Large scale preparative work used the 4-chlorophenylsulfonate (**9a**).



8

9a X= Cl
9b X= Br
9c X= NO_2

a. 4-X-$PhSO_2Cl$, CH_2Cl, NEt_3 (95%). b. NaCN, DMSO, (90%)

Key intermediate **6** contains both the chiral centers present in CI-981 and can be obtained in an extremely pure form due to its highly crystalline nature. As such, **6** serves as an ideal intermediate for the preparation of CI-981. The three syntheses described here have all been carried out successfully on a multi-kilo scale.

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2. Sirton, C. R., *Phrmacol. Res.*, **1990**, *22*, 555.
3. For example see: a) Coppola, G. M. *Heterocycles* **1989**, *29*, 1497; b) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.*, **1990**, *33*, 21; c) Sliskovic D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.*, **1990**, *33*, 31; d) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; Kerekjarto, B. v.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.*, **1990**, *33*, 52; e) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Kerekjarto, B. v.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.*, **1990**, *33*, 61; f) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.*, **1990**, *33*, 758; g) Sit, S. Y.; Parker, R. A.; Motoc, I.; Han, W.; Balasubramanian, N.; Cat, J. D.; Brown, P. J.; Harte, W. E.; Thompson, M. D.; Wright, J. J. *J. Med. Chem.*, **1990**, *33*, 2982; h) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W., *J. Med. Chem.*, **1991**, *34*, 357; i) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson, E.; Krause, B. R.; Newton, R. S.; Sekerke C.; Shaw, M. K., *J. Med. Chem.*, **1991**, *34*, 367 and references therein.
4. For example see: a) Rosen, T. and Heathcock, C. H., *Tetrahedron*, **1986**, *42*, 4909; b) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I., *Tetrahedron Lett.* **1987**, *28*, 1385; c) Roth, B. D.; Roark, W. H.; *Tetrahedron Lett.* **1988**, *29*, 1255; d) Prasad, K.; Chen, K.-M.; Repic, O.; Hardtmann, G. E., *Tetrahedron: Asymmetry*, **1990**, *1*, 307; e) Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, h.; Schnierer, M., *Tetrahedron Lett.*, **1990**, *31*, 2545; f) Cardani, S.; Scolastico, C.; Villa, R., *Tetrahedron Lett.*, **1990**, *31*, 7283; g) Ballini, R.; Marcantoni, E.; Petrini, M., *J. Chem. Soc. Perkin I*, **1991**, 490; h) Bennett, F.; Knight, D. W.; Fenton, G., *J. Chem. Soc. Perkin I*, **1991**, 519; i) Kanegafuchi Chem. KK, *European Patent Application* EP 374-922.
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8. a) *European Patent Application* EP 330-172-A. b) Compound (**4**) was prepared from either the methyl, ethyl or n-butyl ester of (S)-4-bromo-3-hydroxybutyric acid. See Sletzinger, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M. H., *Tetrahedron Lett.*, **1985**, *26*, 2951; c) The preparation of the enantiomer of (**4**) has been reported; *U.S. Pat.* 4,611,067.

9. ^{1}H NMR spectrum of **4a** (200 MHz, in $CDCl_3$) δ 0.09 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 2.63 (m, 4H), 3.70 (s, 3H), 4.38 (m, 1H); $[\alpha]_D$ -20.5° (c=1, $CHCl_3$). FTIR and Mass Spectral data were in accord with the structure.
^{1}H NMR spectrum of **4b** (200 MHz, in $CDCl_3$) δ 0.09 (s, 3H), 0.15 (s, 3H), 0.89 (s, 9H), 1.27 (t, J=7.1 Hz, 3H), 2.62 (m, 4H), 4.15 (q, J=7.3, 2H), 4.38 (m, 1H); $[\alpha]_D$ -16.8° (c=1.06, $CHCl_3$). Elemental analysis, FTIR and Mass Spectral data were in accord with the structure.
^{1}H NMR spectrum of **4c** (200 MHz, in $CDCl_3$) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.84 (s, 9H), 0.92 (t, 3H), 1.33 (q, J=7.8, 2H), 1.55 (q, J=7.8, 2H), 2.56 (m, 4H), 4.30 (m, 2H), 4.32 (m, 1H); $[\alpha]_D$ -15.1° (c=1, $CHCl_3$). Elemental analysis, FTIR and Mass Spectral data were in accord with the structure.
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11. ^{1}H NMR spectrum of **5** (200 MHz, in $CDCl_3$) δ 1.48 (s, 9H), 2.62 (m, 2H), 2.89 (d, J=6.1 Hz, 2H), 3.43 (s, 2H), 4.41 (pentet, J=6.1 Hz, 2H). ^{13}C NMR, FTIR and Mass Spectral data were in accord with structure.
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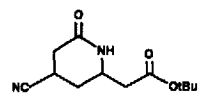
13. ^{1}H NMR spectrum of **6** (200 MHz, in $CDCl_3$) δ 1.36 (m, 1H), 1.42 (s, 3H), 1.49 (s, 9H), 1.50 (s, 3H), 1.79 (dt, J=2.5 and 12.1 Hz, 1H), 2.40 (dd, J=6.2 and 15.4 Hz, 1H), 2.5-2.7 (m, 1H), 2.55 (d, J=6.1 Hz, 2H), 4.18 (m, 1H), 4.32 (m, 1H); m.p. 67.2-69.7 C; $[\alpha]_D$ 1.33 (c=1, $CHCl_3$). Elemental analysis, ^{13}C NMR, FTIR and Mass Spectral data were in accord with the structure.
14. Enantiomeric purities (i.e. ratios of 3R,5R:3S,5S) were determined by HPLC at 225 nm using a 25 cm Chiracel OD column, with a mobile phase of hexane-IPA (95:5) at a flow rate of 1 ml/min. Diastereomeric ratios (i.e. 3R,5R:3S,5R) were determined by VPC. Accurate determination of the enantiomeric purity of **6** was achieved by independant, unambiguous syntheses of the 3S,5S and 3S,5R stereoisomers.
15. ^{1}H NMR spectrum of **7a** (200 MHz, in $CDCl_3$) δ 2.65 (m, 4H), 3.74 (s, 3H), 3.77 (d, 1H), 4.37 (m, 1H); $[\alpha]_D$ -35.5° (c=1, $CHCl_3$).
^{1}H NMR spectrum of **7b** (200 MHz, in $CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H), 2.64 (m, 4H), 3.75 (brs, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.36 (m, 1H); $[\alpha]_D$ -33.1° (c=1.2, $CHCl_3$). FTIR and Mass Spectral data were in accord with the structure.
^{1}H NMR spectrum of **7c** (200 MHz, in $CDCl_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.38 (m, 2H), 1.61 (m, 2H), 2.64 (m, 4H), 3.81 (brs, 1H), 4.13 (t, J=6.6, 2H), 4.36 (m, 1H); $[\alpha]_D$ -26.7° (c=1.34, $CHCl_3$). FTIR and Mass Spectral data were in accord with the structure.
16. Available from Kaneka America in ≥98% ee.
17. Sunay, U.; Fraser Reid B., *Tetrahedron Lett.*, **1986**, *27*, 5335.
18. The iodide (prepared from the sulfonates (**9**) with NaI/Acetone or directly from **8** by the method described by Classon, B.; Liu, Z. and Samuelsson, B., *J. Org. Chem.*, **1988**, *53*, 6126) was also converted to **6** but in lower overall yields.
19. Heating in the presence of excess cyanide led to extensive decomposition. A precipitated solid was identified as the δ-lactam (**A**).



A

^{1}H NMR spectrum of **A** (360 MHz, in $CDCl_3$) δ 1.45 (s, 9H), 1.55 (m, 1H), 2.20 (m, 1H), 2.40 (m, 2H), 2.60 (m, 2H), 2.80 (m, 1H), 4.00 (m, 1H), 6.60 (brs, 1H, exc with D_2O). Elemental analysis, ^{13}C NMR, FTIR and Mass Spectral data were in accord with the structure.

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