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A new approach to the synthesis of a polyfunctional acyclic chiral building block based on ethyl (*S*)-(–)-lactate

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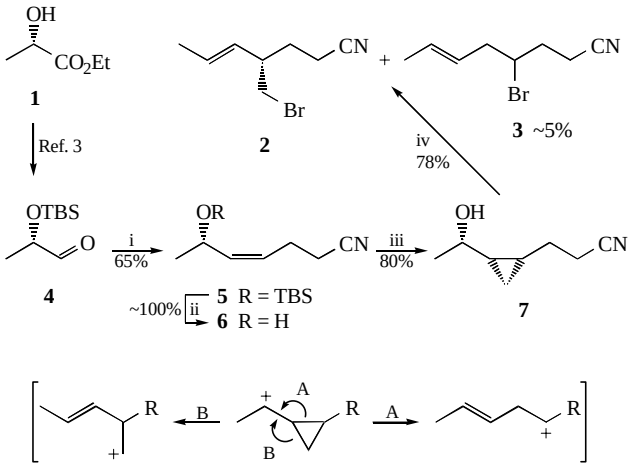
Based on ethyl (*S*)-(–)-lactate, an original sequence of highly stereoselective transformations leading to (4*S*,5*E*)-4-bromomethylhept-5-enenitrile was developed using rearrangement of a chiral cyclopropyl carbinol as the key step.

Chiral acyclic building blocks are important intermediates in the syntheses of various natural compounds (see, for example, ref. 1). In this paper, we consider a new approach to the stereocontrolled synthesis of these compounds on the basis of commercially available ethyl (*S*)-(–)-lactate **1**. This approach is illustrated by the transformation of **1** into chiral nitrile **2**. An attractive feature of compound **2** as a building block is the possibility of selective transformation of any of functionalised hydrocarbon substituents that form its stereogenic centre.

The key step of the synthesis of nitrile **2** was the rearrangement of cyclopropyl carbinol **7** under the action of $ZnBr_2$ in the presence of Me_3SiBr (*cf.* ref. 2). Compound **7** was synthesised from ester **1** (ee > 99%, Merck) as a result of a sequence of almost stereospecific reactions. This sequence includes a well-known two-step transformation of **1** into aldehyde **4**,[3] olefination of **4** using phosphorane **8**, which was prepared under salt-free conditions [$NaN(SiMe_3)_2$, THF, –30 → 0 °C, 0.5 h; *cf.* ref. 4] from a corresponding phosphonium salt,[5] to form (*Z*)-olefin **5** (*Z* > 99%, ^{1}H and ^{13}C NMR data) and cyclopropanation of allyl alcohol **6** according to the Simmons–Smith reaction with high diastereoselectivity characteristic of this reaction[6] (**7**: de > 99%, ^{1}H and ^{13}C NMR data).



Scheme 1 *Reagents and conditions*: i, $Ph_3P{=}CH(CH_2)_2CN$ **8**, THF, –78 → → 0 °C, 1 h; ii, $Bu_4N^+F^-$, THF, 20 °C, overnight; iii, CH_2I_2, $ZnEt_2$, CH_2Cl_2, 20 °C, 48 h; iv, $ZnBr_2$, TMSBr, CH_2Cl_2, –30 → 0 °C, 30 min.

Note that the found regioselectivity of the rearrangement of cyclopropyl carbinol **7** was not observed previously for related structures. Of the two possible directions (A and B, see Scheme 1) of the cleavage of a cyclopropane ring with an additional alkyl substituent, only A usually occurs. The preference of this reaction path was explained by the formation of a more stable secondary carbocation; the addition of a nucleophile to this carbocation results in corresponding linear product like **3**.[7]

In the case of cyclopropyl carbinol **7**, under the conditions chosen for the rearrangement, branched product **2** was formed almost solely. There is no reasonable explanation for this anomalous reaction path for **7**, and we shell attempt to explain this phenomenon later on.

The structures of previously unknown compounds **2**, **5**–**7** were confirmed by elemental analysis and spectroscopic data.† According to the GC–MS data, nitrile **2** contains an isomeric impurity (~5%), which is linear product **3**, as follows from the presence of the signal of corresponding integral intensity of the CHBr proton (m, 3.98–4.15 ppm) in the ^{1}H NMR spectrum of **2**.

It is evident that nitrile **2** prepared in this manner is of high enantiomeric purity, because each of the steps **1**→**4**→**5**→**6**→**7** is virtually stereospecific, whereas the final rearrangement **6**→**7** proceeds without the participation of the chiral centre, which ultimately remains in the molecule of **2**.

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† *(4S,5E)-4-Bromomethylhept-5-enenitrile* **2**: $[\alpha]_D^{16}$ = 45.1 (*c* 1.21, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.50–1.70 (m, 1H, 3-H), 1.72 (dd, 3H, 7-Me, *J* 6.5 and 1.6 Hz), 1.92–2.12 (m, 1H, 3-H), 2.22–2.55 (m, 3H, 2-H and 4-H), 3.28–3.50 (m, 2H, CH_2Br), 5.19 (ddq, 1H, 5-H, *J* 15.3, 8.8 and 1.6 Hz) 5.67 (dq, 1H, 6-H, *J* 15.3 and 6.5 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 15.01 (C-2), 17.93 (C-7), 28.62 (C-3), 37.57 (CH_2Br), 43.50 (C-4), 119.28 (C-1), 129.48 (C-6), 130.15 (C-5). IR (neat, ν/cm^{-1}): 650, 800, 930, 975, 1225, 1245, 1270, 1305, 1370, 1430, 1450, 1668, 2260, 2860, 2940, 2980, 3030. Found (%): C, 47.66; H, 6.05; Br, 39.29; N, 6.91. Calc. for $C_8H_{12}BrNO$ (%): C, 47.55; H, 5.98; Br, 39.54; N, 6.93.

(4Z,7S)-7-(tert-Butyldimethylsilyloxy)hept-4-enenitrile **5**: $[\alpha]_D^{18}$ = 29.7 (*c* 2.46, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.05 and 0.06 (s, 6H, MeSi), 0.89 (s, 9H, Bu^t), 1.22 (d, 3H, Me, *J* 6.3 Hz), 2.30–2.55 (m, 4H, 2-H and 3-H), 4.58 (dqd, 1H, 6-H, *J* 8.1, 6.3 and 1.1 Hz), 5.20–5.35 (m, 1H, 4-H, $J_{4\text{-H},5\text{-H}}$ 11.1 Hz, $J_{4\text{-H},6\text{-H}}$ 1.1 Hz), 5.52–5.67 (m, 1H, 5-H, $J_{5\text{-H},6\text{-H}}$ 8.1 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: –4.68 and –4.54 (MeSi), 17.46 (C-2), 18.11 (*C*Me$_3$), 23.69 (C-3), 23.79 (C-7), 25.78 (C*Me*$_3$), 64.98 (C-6), 119.03 (CN), 123.29 (C-4), 138.46 (C-5). IR (neat, ν/cm^{-1}): 675, 745, 785, 820, 845, 890, 945, 1000, 1015, 1045, 1090, 1137, 1190, 1260, 1305, 1335, 1365, 1370, 1390, 1410, 1430, 1448, 1465, 1475, 2260, 2865, 2900, 2940, 2960, 3020.

(4Z,7S)-7-Hydroxyhept-4-enenitrile **6**: $[\alpha]_D^{24}$ = –7.8 (*c* 1.83, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.24 (d, 3H, Me, *J* 6.3 Hz), 2.30–2.63 (m, 4H, 2-H and 3-H), 4.57 (dqd, 1H, 6-H, *J* 8.1, 6.3 and 1.1 Hz), 5.30–5.50 (m, 1H, 4-H), 5.55–5.68 (m, 1H, 5-H). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 17.49 (C-2), 23.41 (C-3 and C-7), 63.29 (C-6), 119.42 (CN), 125.60 (C-4), 137.36 (C-5). IR (neat, ν/cm^{-1}): 760, 840, 875, 935, 1030, 1065, 1105, 1135, 1195, 1225, 1290, 1315, 1370, 1430, 1450, 2655, 2260, 2915, 2975, 3020, 3400. Found (%): C, 67.25; H, 8.79; N, 11.37. Calc. for $C_7H_{11}NO$ (%): C, 67.17; H, 8.85; N, 11.19.

(1S,1″S,2R)-2-(2′-Cyanoethyl)-1-(1″-hydroxyethyl)cyclopropane **7**: $[\alpha]_D^{16}$ = –38.4 (*c* 2.06, MeOH). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.17–0.26 (m, 1H, *cis*-3-H), 0.76–0.88 (m, 1H, *trans*-3-H), 0.88–1.06 (m, 2H, 1-H and 2-H), 1.29 (d, 3H, 2″-Me, *J* 6.1 Hz), 1.40 and 1.95 (m, 2H, 1′-H), 2.35–2.45 (m, 2H, 2′-H), 3.37 (dq, 1H, 1″-H, *J* 8.5 and 6.1 Hz). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ: 9.34 (C-3), 15.17 (C-2), 17.49 (C-2′), 23.77, 24.03 (C-1 and C-2″), 24.85 (C-1′), 68.21 (C-1″), 119.64 (C-3′); IR (neat, ν/cm^{-1}): 860, 890, 920, 940, 980, 1005, 1025, 1085, 1105, 1138, 1180, 1375, 1425, 1455, 2260, 2930, 2985, 3000, 3170, 3400. Found (%): C, 69.37; H, 9.54; N, 9.84. Calc. for $C_8H_{13}NO$ (%): C, 69.03; H, 9.41; N, 10.06.

References

1 (*a*) U. Berens and H.-D. Schart, *Synthesis*, 1991, 832; (*b*) B. A. Czeskis, N. A. Shpiro and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1991, 2529 (*Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1991, **40**, 2205); (*c*) K. Mori, in *The Total Synthesis of Natural Products*, ed. J. A. Simon, Wiley, New York, 1992, vol. 9; (*d*) C. H. Senanayake, R. D. Larsen, T. J. Bill, J. Liu, E. G. Corley and P. J. Reider, *Synlett*, 1994, 199.

2 A. M. Moiseenkov, B. A. Czeskis, N. M. Ivanova and O. M. Nefedov, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2639.

3 M. Hirama, T. Shigemoto and S. Ito, *J. Org. Chem*., 1987, **52**, 3342.

4 (*a*) H. J. Bestmann, T. Brosche, K. H. Koschatzky, K. Michaelis, H. Platz, O. Vostrowsky and W. Knauf, *Tetrahedron Lett*., 1980, **21**, 747; (*b*) P. Vinczer, G. Baan, L. Novak and C. Szantay, *Tetrahedron Lett*., 1984, **25**, 2701.

5 J. H. Wagenknecht and M. M. Baizer, *J. Org. Chem*., 1966, **31**, 3885.

6 (*a*) A. B. Charette and J.-F. Marcoux, *Synlett*, 1995, 1197; (*b*) M. Lautens and P. H. M. Delanghe, *J. Org. Chem*., 1995, **60**, 2474.

7 (*a*) M. Julia, S. Julia and J. A. du Chaffaut, *Bull. Soc. Chim. France*, 1960, 1735; (*b*) M. Hanack and H. Eggensperger, *Chem. Ber*., 1963, **96**, 1259; (*c*) B. A. Czeskis and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1982, 2545 (*Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1982, **31**, 2245); (*d*) A. M. Moiseenkov, B. A. Czeskis and A. V. Semenovsky, *J. Chem. Soc., Chem. Commun*., 1982, 109; (*e*) A. M. Moiseenkov, B. A. Czeskis, I. G. Bolesov, G. R. Zhurina, K. Jernstedt and G. Ahlgren, *Chem. Scr.*, 1982, **19**, 182.

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