Synthesis of Enantiomerically Pure Bicyclo[3.1.0]hexanes from D-Ribose by Intramolecular Cyclopropanation

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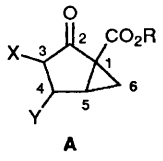
Highly functionalized optically pure bicyclo[3.1.0]hexan-2-ones **6a** and **6b** are easily obtained by the intramolecular cyclopropanation of a D-ribose derivative using the iodonium ylide or diazo compound methods, which afford the final products with opposite diastereoselectivities.

Bicyclo[3.1.0]hexane derivatives of the general structure **A** are of considerable importance in organic synthesis due to the versatility of the cyclopropane ring[1] and the ubiquitous occurrence of the cyclopentane ring in natural products and synthetic materials.[2] These and related systems have been extensively used as intermediates in the synthesis of steroids,[3] prostanoids,[4] vitamin D analogues,[5] terpenoids[6] and amino acids.[7] Furthermore, the bicyclo[3.1.0]hexane ring system, properly substituted, has been used as the carbocyclic moiety for the synthesis of modified nucleosides structurally related to neplanocin C.[8]



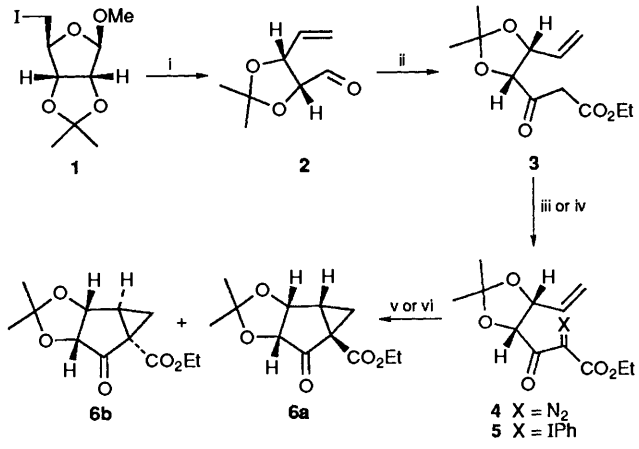
A

The most general method used for the construction of the ring system **A** is the intramolecular cyclopropanation of unsaturated diazocarbonyl compounds, which act as carbenoid precursors.[9] However, the use of iodonium ylides[5g,10] instead of the hazardous diazo compounds has also been proposed. Several methods have been utilized for the preparation of optically active bicyclo[3.1.0]hexanes. They include the resolution of racemates,[5c,d] the enantioselective intramolecular carbene–olefin cyclopropanation using diazocarbonyl compounds in the presence of chiral catalysts,[5e,11] the diastereoselective Simmons–Smith reaction[12] and the intramolecular cyclopropanation *via* iodonium ylides using chiral auxiliary alcohols.[5g]

We now report a different approach to enantiomerically pure bicyclo[3.1.0]hexane derivatives by the intramolecular cyclopropanation of sugar templates using the diazocarbonyl and iodonium ylide methods.

The unsaturated aldehyde **2** was easily prepared by refluxing an ethanolic solution of the iodoribose derivative **1** with activated zinc,[13] removal of the solids by filtration and careful evaporation of the solvent at temperatures[14] not exceeding 35 °C. Treating a methylene dichloride solution of compound **2** with ethyl diazoacetate in the presence of tin chloride[15] at room temp. for 2 h gave the keto ester **3** in 46% yield from compound **1**. Any remaining alcohol from the former step degrades the yield of compound **3**, since it reacts preferentially with ethyl diazoacetate to form the *O*-ethyl glycolic acid ethyl ester. The unsaturated keto ester **3** was then converted by standard procedures either to the diazo compound **4** in quantitative yield[6d] or to the iodonium ylide **5**,[10a] which was not characterized because of its instability, but was used immediately in the next reaction.†

The diazo compound **4** underwent intramolecular cyclopropanation by refluxing in toluene for 6 h in the presence of a catalytic amount of CuI (5 mol%) to give the desired bicyclo[3.1.0]hexan-2-one derivatives **6a** and **6b** in 66% total yield and with a diastereoisomeric ratio of 4.5:1. On the other hand, the iodonium ylide **5** was cyclized by stirring in methylene dichloride at room temp. for 1 h in the presence of a catalytic amount of CuI (5 mol%), to give compounds **6a** and **6b** in 45% total yield (from compound **3**) and with a diastereoisomeric ratio of 1:1.5. Diastereoisomers **6a** and **6b** were easily separated by column chromatography on silica gel (ethyl acetate–hexane 1:2, $\Delta R_f = 0.1$).† The structural assignment of the diastereoisomers was based on their ^{1}H NMR spectra, where the proton coupling constant $J_{4,5}$ was zero for compound **6b** and 5.5 Hz for compound **6a**. In related systems, the $J_{4,5}$ is zero when the two protons are in *anti* positions.[8a]



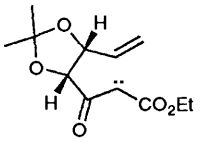
Scheme 1 *Reagents and conditions:* i, Zn, EtOH (95%), reflux, 1 h; ii, N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, room temp., 2 h, 46% from **1**; iii, TsN_3, Et_3N, room temp., 6 h, 97% to **4**; iv, $PhI(OAc)_2$, KOH (4 quiv.), EtOH, −5 °C (to **5**); v, CuI, toluene, reflux, 6 h (for **4**); vi, CuI, CH_2Cl_2, N_2, room temp., 1 h (for **5**)

An interesting feature of the reactions reported here is the reverse diastereoselectivity obtained by the diazo compound and the iodonium ylide. This finding supports Moriarty's suggestion[5g,10] that these two reactions follow different mechanisms: the metal-catalysed decomposition of the diazo compounds probably proceeds *via* a carbenoid, while the iodonium ylide cyclopropanation is a stepwise electrophilic

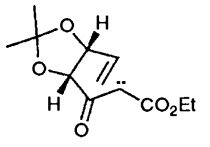
† All new compounds isolated **3**, **4**, **6a** and **6b** gave satisfactory elemental analyses or exact molecular weight measurements. $[\alpha]_D$ Values are given in uhits of 10^{-1} deg cm^2 g^{-1}. Compound **3**: oil, $[\alpha]_D$ +37 (*c* 1 in $CHCl_3$); compound **4**: oil, $[\alpha]_D$ −72 (*c* 1 in $CHCl_3$); compound **6a**: oil, $[\alpha]_D$ −44.2 (*c* 0.67 in $CHCl_3$); compound **6b**: oil, $[\alpha]_D$ −36.6 (*c* 0.64 in $CHCl_3$). ^{1}H NMR data (*J*/Hz): compound **6a**: $\delta_H(CDCl_3)$ 1.25 (3 H, t, *J* 7), 1.3 (3 H, s), 1.5 (3 H, s), 1.8 (1 H, t, *J* 5.5, 6-H), 2.05 (1 H, dd, *J* 8.5 and 5.5, 6-H), 2.75 (1 H, dt, *J* 8.5 and 5.5, 5-H), 4.2 (2 H, q, *J* 7), 4.35 (1 H, d, *J* 8, 3-H) and 5.05 (1 H, dd, *J* 8 and 5.5, 4-H); compound **6b**: $\delta_H(CDCl_3)$ 1.25 (3 H, t, *J* 7), 1.35 (3 H, s), 1.4 (3 H, s), 1.55 (1 H, t, *J* 5.5, 6-H), 2.1 (1 H, dd, *J* 8.5 and 5.5, 6-H), 2.85 (1 H, dd, *J* 8.5 and 5.5, 5-H), 4.2 (2 H, q, *J* 7), 4.3 (1 H, d, *J* 5, 3-H) and 4.7 (1 H, d, *J* 5, 4-H).

addition of the iodonium centre to the double bond. This then affords the cyclopropane ring by reductive elimination of iodobenzene through an intermediate analogous to intermediates **I-1** and **I-2**. In the present case, the favoured transition state **TS-1** from the carbenoid and the unfavoured intermediate **I-1** from the iodonium ylide give the product **6a**, while the unfavoured **TS-2** and the favoured intermediate **I-2** give the product **6b**.

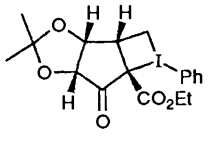
This synthetic route could also be used to prepare the enantiomers of **6a** and **6b**, since the enantiomer of aldehyde **2** is also known.[14,16]



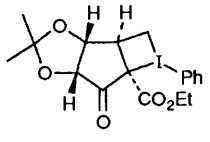
TS-1



TS-2



I-1



I-2

Experimental

Synthesis of the Keto Ester **3** *from the Iodoribose* **1**.—To a well stirred solution of compound **1** (1.256 g, 4 mmol) in EtOH (95%; 20 cm^3) was added activated zinc[13] (2.6 g, 40 mmol). The mixture was refluxed for 1 h whilst the reaction progress was monitored by TLC. The solids were then filtered off and the solvent was carefully evaporated under reduced pressure with the bath temperature not exceeding 35 °C. The product was dissolved in CH_2Cl_2 (10 cm^3), $SnCl_2$ (760 mg) and ethyl diazoacetate (570 mg, 5 mmol) were added and the mixture stirred at room temp. for 2 h. The desired keto ester **3** (445 mg, 46%) was obtained by chromatography on silica gel (ethyl acetate–hexane, 1:4).

Bicyclo[3.1.0]*hexan-2-ones* **6a** *and* **6b**.—(*i*) *From the diazo compound* **4**. To a well stirred solution of the diazo compound **4** (268 mg, 1 mmol) in toluene (5 cm^3), prepared according to the literature procedure[6d] from compound **3**, was added CuI (10 mg) and the resultant mixture was refluxed for 6 h. Column chromatography of the reaction mixture on silica gel (ethyl acetate–hexane 1:2) gave compound **6a** (130 mg, 54%) followed by compound **6b** (29 mg, 12%).

(*ii*) *From the iodonium ylide* **5**. To a cold stirred solution of the keto ester **3** (242 mg, 1 mmol) in EtOH (5 cm^3) was added at −5 °C a solution of KOH (224 mg, 4 mmol) in EtOH (5 cm^3) followed by the addition at the same temp. of a solution of $PhI(OAc)_2$ (322 mg, 1 mmol) in EtOH (10 cm^3). The mixture was kept at −5 °C for 30 min, then poured into H_2O (20 cm^3), extracted with CH_2Cl_2 (2 × 50 cm^3) and the organic layer was dried over $MgSO_4$. The solution was concentrated to 10 cm^3 and then CuI (10 mg) was added and the mixture was stirred at room temp. for 1 h, under a nitrogen atmosphere. Compounds **6a** and **6b** formed, and were isolated as above in yields of 18% (43 mg) and 27% (65 mg), respectively.

References

1 (*a*) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; (*b*) *The Chemistry of the Cyclopropyl Group*, Z. Rappoport, Wiley, New York, 1987, Parts 1 and 2; (*c*) T. Hudlicky and J. W. Reed, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 5, p. 899.

2 (*a*) E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989; (*b*) S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983; (*c*) A. D. Borthwick and K. Biggedike, *Tetrahedron*, 1992, **48**, 571; (*d*) T. Hudlicky and J. D. Price, *Chem. Rev.*, 1989, **89**, 1467.

3 B. M. Trost, D. F. Taber and J. B. Alper, *Tetrahedron Lett.*, 1976, **17**, 3857.

4 (*a*) K. Kondo, E. Hiro and D. Tunemoto, *Tetrahedron Lett.*, 1976, **17**, 4499; (*b*) D. F. Taber, *J. Am. Chem. Soc.*, 1977, **99**, 3513.

5 (*a*) H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto and T. Kametani, *Tetrahedron Lett.*, 1983, **24**, 4257; (*b*) H. Nemoto, X.-M. Wu, H. Kurobe, M. Ihara, K. Fukumoto and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 3095; (*c*) H. Nemoto, X.-M. Wu, H. Kurobe, K. Minemura, M. Ihara, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1185; (*d*) S. R. Wilson, M. S. Haque, A. M. Venkatesan and P. A. Zucker, *Tetrahedron Lett.*, 1984, **25**, 3151; (*e*) S. R. Wilson, A. M. Venkatesan, C. E. Angelli-Szafran and A. Yasmin, *Tetrahedron Lett.*, 1991, **32**, 2339; (*f*) M. Kabat, J. Kiegiel, N. Cohen, K. Toth, P. M. Wovkilivich and M. R. Uskokovic, *Tetrahedron Lett.*, 1991, **32**, 2343; (*g*) R. M. Moriarty, J. Kim and L. Guo, *Tetrahedron Lett.*, 1993, **34**, 4129.

6 (*a*) T. Hudlicky, B. C. Ranu, S. M. Naqvi and A. Srnak, *J. Org. Chem.*, 1985, **50**, 123; (*b*) E. Y. Chen, *J. Org. Chem.*, 1984, **49**, 3245; (*c*) S. H. Kang, W. J. Kim and Y. B. Chae, *Tetrahedron Lett.*, 1988, **29**, 3169; (*d*) A. J. Singh, R. K. Bakshi and E. J. Corey, *J. Am. Chem. Soc.*, 1987, **109**, 6187.

7 (*a*) A. M. P. Koskinen and L. Muñoz, *J. Chem. Soc., Chem. Commun.*, 1991, 1373; (*b*) A. M. P. Koskinen and L. Muñoz, *J. Org. Chem.*, 1993, **58**, 879; (*c*) A. M. R. Koskinen and H. Hassila, *J. Org. Chem.*, 1993, **58**, 4479.

8 (*a*) J. B. Rodriguez, V. E. Marquez, M. C. Nicklaus and J. J. Barchi, Jr., *Tetrahedron Lett.*, 1993, **34**, 6233; (*b*) L. H. Koole, S. Neidle, M. D. Crawford, A. A. Krayevski, G. V. Gurskaya, A. Sandstrom, J.-C. Wu, W. Tong and J. Chattopadhaya, *J. Org. Chem.*, 1991, **56**, 6884.

9 A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385.

10 (*a*) R. M. Moriarty, O. Prakash, R. K. Vaid and L. Zhao, *J. Am. Chem. Soc.*, 1989, **111**, 6443; (*b*) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH Publishers, Weinheim, 1992, p. 323.

11 W. G. Dauben, R. T. Hendricks, M. J. Luzzio and H. P. Ng, *Tetrahedron Lett.*, 1990, **31**, 6969.

12 (*a*) C. R. Johnson and M. R. Barbachyn, *J. Am. Chem. Soc.*, 1982, **104**, 4290; (*b*) E. A. Mash and K. A. Nelson, *J. Am. Chem. Soc.*, 1985, **107**, 8256; (*c*) E. A. Mash and K. A. Nelson, *Tetrahedron Lett.*, 1986, **27**, 1441; (*d*) E. A. Mash and D. S. Torok, *J. Org. Chem.*, 1989, **54**, 250; E. A. Mash, S. B. Hemperly, K. A. Nelson, P. C. Heidt and S. Van Deusen, *J. Org. Chem.*, 1990, **55**, 2045.

13 See preceding paper.

14 T. V. RajanBabu, W. A. Nuget, D. F. Taber and P. J. Fagan, *J. Am. Chem. Soc.*, 1988, **110**, 7128.

15 C. R. Holquist and E. J. Roskamp, *J. Org. Chem.*, 1989, **54**, 3258.

16 A. Fürstner, D. Jumbam, J. Teslic and H. Weidmann, *J. Org. Chem.*, 1991, **56**, 2213.

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