Multiple Equilibration Strategies in Synthesis. Stereocontrolled Synthesis of Polypropionate Fragments

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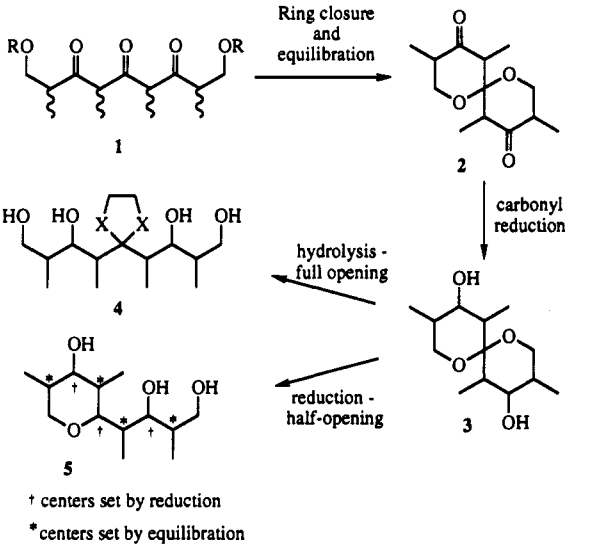
Received December 4, 1992

Summary: A multiple equilibration strategy as a general approach to asymmetric synthesis has been demonstrated. The generation, multiple equilibration, and manipulation of methyl-substituted 4,10-diketo-1,7-dioxaspiro[5.5]-undecanes has led to the synthesis of polypropionate fragments containing tetrahydropyran rings containing seven contiguous stereocenters in only five steps with complete stereocontrol.

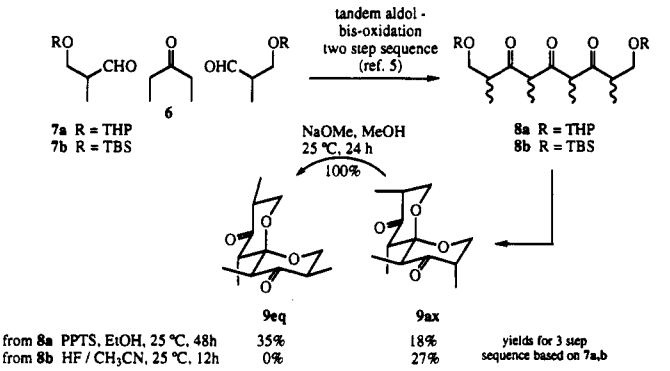
Advances in stereoselective synthesis in the past two decades have been strategically based on the development of kinetic reaction processes. In attempting to control transition state structure, one must accept the limitation that control is being exerted on a relatively small number of atoms and, hence, only a small number of new stereogenic centers may be established in any one process. Thermodynamic processes are not subject to this limitation, yet we are aware of no *general* processes for asymmetric synthesis based on ground-state stereocontrol. We wish to report a process for the synthesis of 9-carbon polypropionate fragments and tetrahydropyran rings which is based on a thermodynamic multiple equilibration to establish several stereogenic centers in a single process.[1,2]

Our general approach to such fragments revolves around the generation and equilibration of methyl-substituted 4,10-diketo-1,7-dioxaspiro[5.5]undecanes (**2**) and is conceptually illustrated in Scheme I. The 1,3,5-trione **1** containing the appropriately blocked hydroxyl groups may be deblocked and allowed to undergo ring closure to a spiroketal **2**. Under the appropriate thermodynamic conditions the spiroketal should equilibrate to the thermodynamically preferred mixture or compound, establishing the relative stereochemistry at five centers including the four methyl-bearing carbons.[3] Controlled reduction of the two carbonyls leads to **3**. Hydrolysis would open the system up to an acyclic 9-carbon fragment **4** while reductive half-opening would lead to a polypropionate fragment incorporating a tetrahydropyran ring **5**. We have accomplished the full sequence leading to tetrahydropyrans **5** in a total of five steps from 3-pentanone.

Scheme I. General Multiple Equilibration Strategy



Scheme II. Multiple Equilibration Sequence



Two equiv of the racemic aldehyde **7a** or **7b**[4] was appended to 3-pentanone via our recently described tandem aldol-bisoxidation sequence[5] to give the triones **8a** and **8b**, respectively, both of which exist extensively in the doubly enolic form as a mixture of two diastereomers. When trione **8b** was treated with HF in CH_3CN for 12 h at 25 °C, only spiroketal **9ax**[6] (of the 16 possible diastereomers) with the two exterior methyl groups in axial orientations was observed. Compound **9ax** was isolated in 27% overall yield from **7b** along with the dihydro-4-pyrone **11** as the only other observable product. This compound probably arises by deacylation of the penultimate spiroketal intermediate **10**. In contrast, removal

(1) Some of these results were described at the 200th Meeting of the American Chemical Society, Washington, DC, 1990; abstract ORGN 135.

(2) An interesting biomimetic and possibly thermodynamic process for assembly of *Daphniphyllum* alkaloids which appears to be general within a limited structural family has been described by Heathcock. For an overview, see: Ruggeri, R.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289. Heathcock, C. H.; Piettre, S.; Kath, J. *Ibid.* **1990**, *62*, 1911. Note also recent equilibration processes in the synthesis of specific compounds: Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686. Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525 and 6529.

(3) Several workers have exploited equilibration at the centers α to the spiro carbon of 1,7-dioxaspiro[5.5]undecanes, although in less functionalized systems in specific syntheses. For a review, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. Vaillancourt, V; Pratt, N. E.; Perron, F.; Albizati, K. F. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley Interscience: New York, 1992; Vol. 8, pp 533–691. Subsequent to our original disclosure (ref 1), a case of 1,7-dioxaspiro-[5.5]undecane equilibration applied to a specific problem was described. See: Totah, N. I.; Schreiber, S. *J. Org. Chem.* **1991**, *56*, 6255.

(4) Francoise Perron, Ph.D. Dissertation, Wayne State University, 1989.

(5) Pratt, N. E.; Zhao, Y.-b.; Hitchcock, S.; Albizati, K. F. *Synlett* **1991**, 361.

(6) The ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data of all new compounds were fully in accord with the proposed structures. For spiroketals **9eq** and **9ax** the structures and conformations as shown were confirmed by X-ray crystallographic analysis. A full discussion of the structural assignments will appear in subsequent publications.

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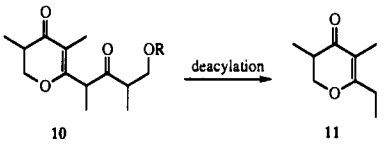


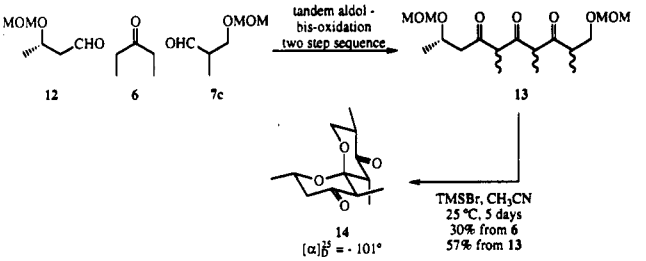
10 11

of the THP blocking groups of **8a** with PPTS in EtOH for 2 days at 25 °C led to **9eq**[6] and **9ax** in 35% and 18% overall yields in the three-step process from **7a**. The anomerically-maximized and strain-minimized spiroketal **9eq** was the predicted thermodynamic product, and it was found that **9ax** could be quantitatively converted to **9eq** with NaOMe in MeOH, confirming this prediction. These three-step sequences can be carried out without purification of intermediates. Although the yields are somewhat modest over the three steps, the increase in molecular complexity[7] based on 3-pentanone is enormous, making these overall yields more than reasonable. The dichotomy of these results is all the more remarkable when it is realized that spiroketals **9eq** and **9ax** possess the same relative stereochemistry at the exterior methyl-group-bearing carbons. The origin of this dichotomy is a current subject of interest. In any case, these stereodifferentiations and the accompanying increases in molecular complexity are remarkable in their efficiency: both spiroketals contain five stereocenters and are available in only three steps from 3-pentanone uncontaminated with other spiroketal isomers.

We have also found that a nonequilibratible center can serve as an anchoring point leading to absolute thermodynamic asymmetric induction via multiple equilibration. Using an analogous aldol-oxidation process, the racemic aldehyde **7c** and the optically pure aldehyde **12**[8] were appended to 3-pentanone to give trione **13**. When treated with 8 equiv of TMSBr in CH_3CN at 25 °C for 5 days, the fully-equilibrated and all-equatorially-substituted spiroketal **14**[6] was isolated in 30% yield. No other spiroketals were observed, although elimination products were detected in several runs.

Equally important to the strategy is the subsequent manipulation of the spiroketals to polypropionate fragments. Stereospecific reductions of the carbonyls was essential because any leakage in stereoselectivity in the reduction of the first carbonyl would probably be multiplied in the reduction of the second. The transformation of spiroketal **9eq** to two stereochemically complementary tetrahydropyran-containing polypropionate fragments is shown in Scheme IV. Stereospecific reduction to diaxial diol **15** was accomplished with L-Selectride (Aldrich) in THF at −78 °C with no other spiroketals observed in the crude reaction product. Analogously, stereospecific reduction to the diequatorial diol **16** was accomplished with potassium in ammonia at low temperature, again with no other products observed. Both of these diols were reductively cleaved stereospecifically with $Et_3SiH/TiCl_4$ to give the tetrahydropyrans **17** and **18**, with the hydride entering into axial orientations on each ring. The structures were supported by coupling constant analysis of the methine protons of the tetrahydropyran ring, indicating equatorial orientations for the methyl groups and the side chains. These complementary polypropionate fragments were available with complete stereocontrol in only five steps from 3-pentanone, demonstrating the potential and versatility of a general multiple equilibration strategy. Further studies on these and other spiroketal templates are currently under investigation in this laboratory.

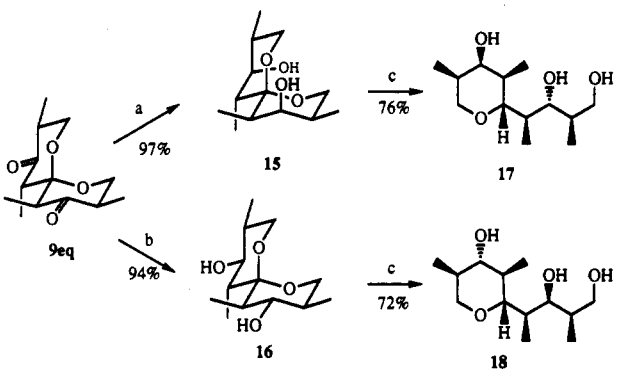
Scheme III. Thermodynamic Asymmetric Induction



12 6 7c 13

14
$[\alpha]_D^{25} = -101°$

Scheme IV. Transformations of Spiroketal 9eq to Complementary Polypropionate Fragments[a]



9eq 15 16 17 18

[a] Key: (a) L-Selectride, THF, −78 °C; (b) K, NH_3, MeOH, −78 °C; (c) Et_3SiH, $TiCl_4$, CH_2Cl_2, −78 °C, followed by stirring with *p*-TsOH in aqueous THF to desilylate partially silylated alcohols.

Acknowledgment. Support for this project was provided by the National Science Foundation (CHE 9120436).

Supplementary Material Available: Procedures and compound characterization data (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801.
(8) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870.