Thermodynamic Spiroketalization as an Efficient Method of Stereochemical Communication

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Summary: A thermodynamically controlled spiroketalization reaction is reported that provides an effective method for controlling the stereochemistry at multiple centers relative to an initial element of stereogenicity.

The ability to control the stereochemical outcome of reaction processes is central to the application of organic synthesis. Of particular importance is the ability to do so in acyclic systems, and recent advances have resulted in a number of effective strategies for achieving this goal.[1] Nevertheless, intermittent cyclic systems are still widely employed to establish structural relationships in open chain targets. The 1,7-dioxaspiro[5.5]undecane system is well suited to such a strategy.[2] In many cases it exists in a single, well-defined conformation, thereby providing a template for kinetically controlled processes.[3] A less obvious feature of this system is, perhaps, its ability to influence the orientational preferences of existing substituents through a process of thermodynamic equilibration.[4] As an extension of these findings, the thermodynamic spiroketalization reaction has been utilized here as a mechanism for remote asymmetric induction.[5] To demonstrate the efficacy of this process we chose to prepare, as a representative example, the C_1–C_9 portion 1 of 6-deoxyerythronolide B.

The required acyclic precursor **2** was prepared by sequential, two-directional homologation of 3-pentanone dimethylhydrazone (Scheme I). The alkyl iodide **3** provided the initial elements of stereochemical control, and the remaining centers were prepared in a stereorandom fashion. Though, theoretically, cyclization of the resulting diastereomeric mixture could produce up to 16 spiroketal isomers, thermodynamic considerations led us to believe that the major component, after equilibration, would have all substituents equatorially disposed.

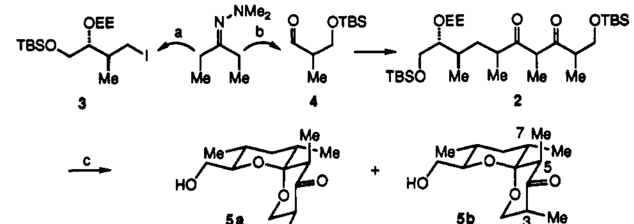
In practice, deprotection and equilibration with camphorsulfonic acid resulted in a 7:1 ratio of two major spiroketal isomers (90% yield) with the expected diastereomer **5a** predominating. The minor component **5b** was epimeric at C_3. Trace amounts (ca. 1%) of a third component, the 3-equatorial-5,7-diaxial system **5c**, were also isolated.[6] Individual isomers **5a** and **5b** were resubjected to the reaction conditions and provided product ratios identical to that originally obtained, indicating that a thermodynamic equilibrium had indeed been established.

The stereochemical control observed herein was anticipated. Ultimate control is provided by the preexistent C_9 and C_{10} stereocenters that serve to anchor the ring system and thereby influence the relative outcome of the forming centers. As demonstrated by Deslongchamps,[4b] the orientation of the C_5 and C_7 methyl groups is linked, with syn isomers resulting in severe steric interactions and anti isomers favoring a diequatorial disposition.

Dissolving metal reduction (Scheme II) then afforded a 10:1 mixture of alcohols with the equatorial isomer predominating. The identity of this product was confirmed by X-ray crystallographic analysis (10), which also served to verify our structural assignment of the preceding spiroketal. The axial alcohol can also be selectively obtained using $LiAlH_4$ in the presence of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide).[7]

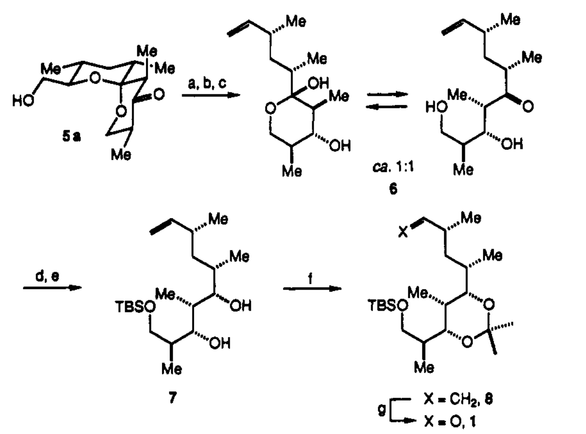
At this point, transformation of the spiroketal to the corresponding acyclic chain was required. Selective io-

Scheme I[a]



[a] i. 1.3 equiv of LDA, THF, 0 °C, 20 h, then **3**, −78 °C; ii. Cu(OAc)$_2$, THF/H_2O (1:1); 92%; (b) i. 1.2 equiv of LDA, THF, −78 °C, 30 min, then **4**, −78 °C, 98%; ii. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; TEA, 74%; (c) i. 0.5 equiv of CSA, CCl_4/MeOH (20:1), reflux, 24 h, 90%; ii. 0.1 M CSA in CCl_4/MeOH (20:1), gentle reflux, 24 h (7:1).

Scheme II[a]



[a] (a) K, NH_3, MeOH, −78 °C, 92% (10:1 mixture); (b) PPh_3, Pyridine, I_2, benzene, 80 °C, 4 h, 81%; (c) Zn, NH_4Cl, EtOH, reflux, 20 min, 100%; (d) TBSCl, iPr$_2$EtN, DMAP, CH_2Cl_2, 72 h, 93%; (e) Bu$_3$B, THF, 25 °C; $NaBH_4$, THF/MeOH (6:1), −78 °C, 8 h; H_2O_2, 93%; (f) 2,2-dimethoxypropane, $CuSO_4$, acetone, 2 h; cat. CSA, 3 h, 83%; (g) O_3, $NaHCO_3$, CH_2Cl_2/MeOH (5:1), −78 °C; DMS, 84%.

(1) For reviews, see: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3–72. (b) Mukaiyama, T., Ed. *Tetrahedron* **1984**, *40*, 2197–2344.

(2) For reviews of spiroketal formation and chemistry, see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699–1740. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.

(3) (a) Pothier, N.; Rowan, D. D.; Deslongchamps, P.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1132–1139. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (c) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauvé, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810, 2814, 2818.

(4) (a) Evans, D. A.; Sacks, D. R.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–6791. (b) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105–1121.

(5) Schreiber, S. L.; Wang, Z. W. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5305.

(6) Structural assignments were made on the basis of ^1H NMR data in conjunction with thermodynamic considerations. MM2 calculations (MACROMODEL) of the corresponding C_9 methyl analogues support these assignments. Still, W. C. et al. *J. Comput. Chem.* **1990**, *11*, 440–467.

(7) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573–4576.

0022-3263/91/1956-6255$02.50/0

dination of the primary alcohol and reductive elimination provided the β-ketoester **6** which exists as a ca. 1:1 mixture of ketone and hemiketal forms. Selective silylation of the primary alcohol effectively trapped this system as its open chain derivative, and subsequent chelation-controlled reduction provided the syn 3,5-diol **7** by a modified Narasaka methodology.[8] While at this point the relative disposition of the hydroxyl groups could not be unequivocally ascertained, the syn assignment was supported by 500-MHz ^{1}H NMR decoupling experiments on the corresponding acetonide **8** and was subsequently confirmed by X-ray crystallography.[9] Ozonolysis provided the aldehyde **1** which corresponds to the C_1–C_9 portion of 6-deoxyerythronolide B.

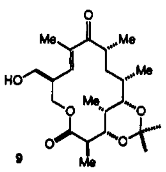
As shown, thermodynamically controlled spiroketalization provides an effective method for controlling the stereochemistry of multiple centers relative to an initial element of stereogenicity. Added flexibility comes from the possible use of the intermittent spiro system as a template for subsequent kinetically controlled transformations. While we chose here to synthesize the C_1–C_9 portion of 6-deoxyerythronolide B, application to a number of other systems may also be possible. Either axial or equatorial hydroxyl functions can be obtained by ketone reduction in the cyclic species, dependent upon the choice of reaction conditions. Further, in the acyclic chain, reduction of a β-ketone function allows access to either syn or anti 1,3-diols. Moreover, spiroketal ring opening by reductive elimination provides a terminal olefin that allows access to a variety of other functional groups.[10]

In summary, the thermodynamic spiroketalization reaction is an effective device for the preparation of distal stereogenic centers. In the example shown, two centers, controlled at an early stage of the sequence, are ultimately responsible for dictating the appropriate stereochemical relationships at five contiguous centers in an acyclic target.[11]

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (GM-32527). We thank Gayle Schulte of the Yale University Instrument Center for determination of X-ray crystal structures.[12]

(8) (a) Narasaka, K.; Pai, F. *Tetrahedron* **1984**, *40*, 2233–2238. (b) Sletzinger, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M. H. *Tetrahedron Lett.* **1985**, *26*, 2951–2954.

(9) The stereochemistry of these centers (C_3 and C_5) was confirmed at a later stage in our synthetic studies by the preparation of lactone **9** as determined by X-ray crystallography. Coordinates are available in the supplementary material. Our studies in this area will be reported elsewhere.



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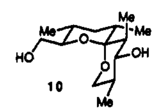
(10) Transketalization is also an option here. See: Schromburg, D.; Hopkins, P. B.; Lipscomb, W. N.; Corey, E. J. *J. Org. Chem.* **1980**, *45*, 1544–1546. Ireland, R. E.; Daub, J. P. *Tetrahedron Lett.* **1982**, *23*, 3471–3474.

(11) This work was taken from the Ph.D. thesis of N. I. Totah, Yale University, 1990.

(12) These structures are the equatorial alcohol **10**, shown below, and lactone **9** (see ref 9). Coordinates are available in the supplementary material.



Direct Syntheses of Polyfused Ring Systems by Intramolecular Tandem Palladium–Ene/Heck Insertion Reactions

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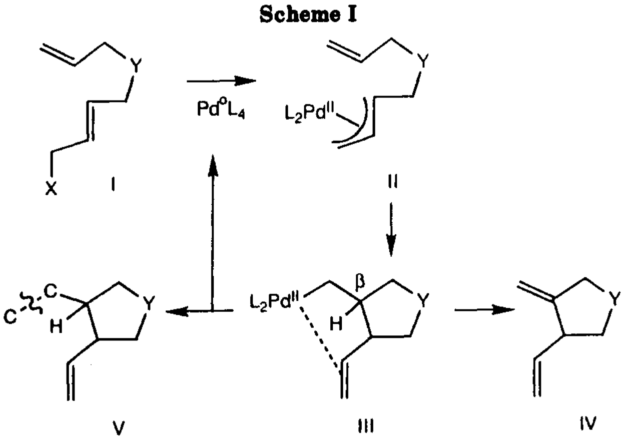
Summary: The Pd(0)-catalyzed polycyclizations **1** → **3** + **4**, **5** → **9** and **6** → **10** are described. The stereospecifity of these transformations is ascribed to an intramolecular suprafacial "palladium–ene" process followed by one to two "Heck-insertions" proceeding with retention of configuration at the metalated carbon.

Palladium- and nickel-catalyzed intramolecular allylations I → IV have been recently shown to provide a variety of carbo- and heterocycles in a stereospecific fashion.[1] The β-elimination step, e.g., III → IV, is relatively fast. Thus, trapping of the transient σ-alkylpalladium species with formation of a new carbon–carbon bond III → V was so far limited to carbonylation reactions.[1]

Scheme I



We report here intramolecular insertions of σ-palladium intermediates III into simple olefinic bonds (Heck inser-

(1) Oppolzer, W.; Gaudin, J.-M. *Helv. Chim. Acta* **1987**, *70*, 1477. Reviews: Oppolzer, W. *Angew. Chem.* **1989**, *101*, 39; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941.