CHIRALITY CONTROLLED BIOMIMETIC OLEFIN CYCLIZATION

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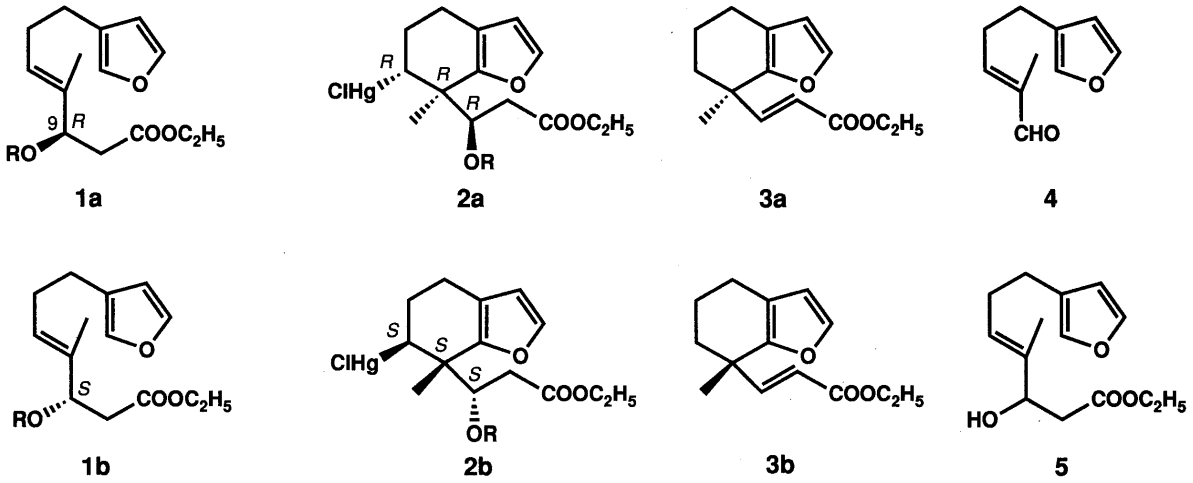
Chiral oxygen functionality located in a polyene chain controls the chirality during mercury (II) triflate induced biomimetic olefin cyclization to give carbocycles under a virtually complete chirality transfer.

KEYWORDS chirality control; diastereoselective; biomimetic; olefin cyclization; mercury triflate; carbamate

Chirality control on a biomimetic olefin cyclization is an important problem in modern organic synthesis, though several approaches have been reported with limited success.[1-5] We have recently described the cyclization of perillene derivatives containing chiral acetal giving rise to carbocycles with 60 to 76 % de[6] by the reaction with mercury triflate.[7,8] In this communication we disclose the cyclization of furano olefins **1a** and **1b**, which contain chiral oxygen functionality at C-9, by mercury triflate to produce carbocycles **2a** and **2b**, respectively, under a virtually complete chirality transfer.

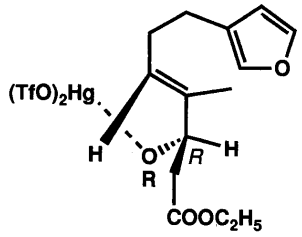


R = $CONHCH(CH_3)C_{10}H_7$-(*S*)

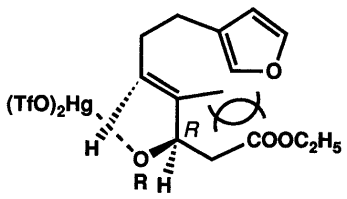
Treatment of optically pure (*S*)-carbamate ethyl ester **1a**, $[\alpha]_D^{22}$ -9.2° (*c* 1.4, $CHCl_3$), with mercury triflate [$Hg(OTf)_2$] (1.2 eq) in dichloromethane at -40 °C for 8 h afforded carbocyclic compound **2a**, mp 171-172 °C, $[\alpha]_D^{22}$ +34.2° (*c* 0.9, $CHCl_3$), as a sole product in 73% yield. The absolute structure of the product **2a** was established through a single crystal X-ray diffraction study to be *R*, *R*, *R* based on the *S*-chirality of carbamate function.[9] At the same time, the C-9 chirality of the starting material **1a** was determined to be *R*. Thus the 9 *R* chirality on the olefinic carbon chain of **1a** induced *R*, *R* asymmetric centers into carbocycle **2a** selectively. The mercury group of **2a** was cleaved by the treatment with $NaBH_4$ in ethanol at -78 °C, and the product was heated at reflux with DBU in toluene for 8 h affording α,β-unsaturated ester **3a**, $[\alpha]_D^{21}$ +1.4° (*c* 0.9, $CHCl_3$), in 60% yield.

Cyclization of diastereomeric **1b** (*S*, *S* isomer), $[\alpha]_D^{22}$ -0.3° (*c* 1.6, $CHCl_3$), with $Hg(OTf)_2$ under the same conditions provided **2b**, $[\alpha]_D^{20}$ -10.7° (*c* 1.1, $CHCl_3$), in 57 % yield. Corresponding α,β-unsaturated ester **3b**, $[\alpha]_D^{22}$ -1.3° (*c* 1.0, $CHCl_3$), was obtained from **2b** by the same operations. Spectral properties of **3b** were indistinguishable from those of **3a** except in the sign of optical rotation.

Regardless of the chirality of the carbamate functionality, cyclization is directed by the oxygen chirality at C-9 in avirtually complete manner. Therefore, two transition state models **A** and **B** were imagined for the cyclization of 9*R* olefin **1a**. Transition state **A** affords *RRR* product **2a**, whereas **B** leads to the diastereomeric *RSS* product. The transition state **B** is reinforced to align ethyl acetate residue and vinyl methyl group in an eclipsed conformation, whereas the methyl group of the transition state **A** is eclipsed with hydrogen. Therefore the energetic preference of **A** over **B** directs the course of cyclization.



A

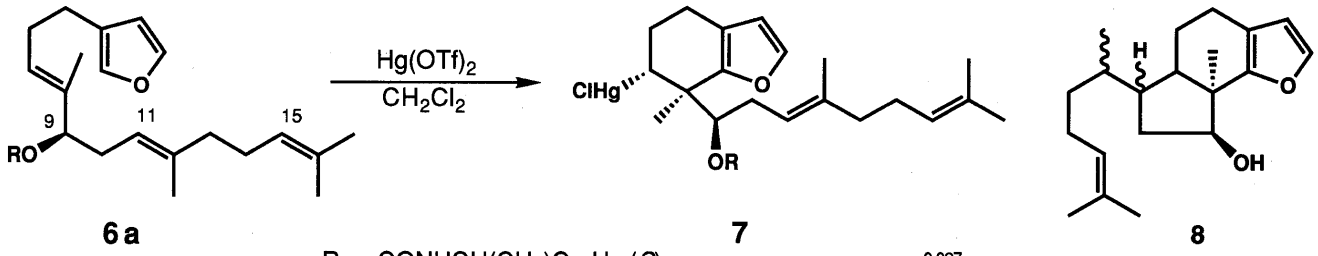


B

Syntheses of **1a** and **1b** have been accomplished from aldehyde **4** derived from perillene. An anion derived from ethyl acetate was treated with **4**, affording racemic carbinol **5**. Reaction of **5** with (*S*)-(+)-1-(naphthyl)ethyl isocyanate and 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene under reflux for 2 days afforded a mixture of **1a** and **1b** in 90% yield. The mixture was subjected to HPLC (YMC D-Sil-5, 20 x 250 mm column, eluted with 11:1 mixture of hexane and ethyl acetate) to give *SR* isomer **1a** and *SS* isomer **1b**.

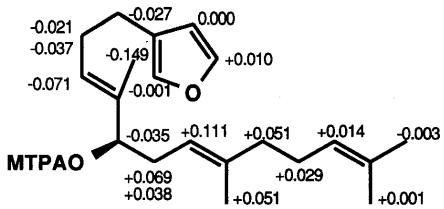
Analogous geranyl homologues **6a**, $[\alpha]_D^{21}$ -8.6° (*c* 1.0, $CHCl_3$), and **6b**, $[\alpha]_D^{21}$-6.2° (*c* 1.1, $CHCl_3$), were also prepared from **4** by a sequential treatment: 1) Me_3SiCN/KCN/18-Crown-6, 2) HCl, 3) ethyl vinyl ether/PPTS, 4) LDA then geranyl bromide, 5) PPTS/MeOH, 6) K_2CO_3, 7) $LiAlH_4$, 8) (*S*)-(+)-1-(naphthyl)ethyl isocyanate, and 9) HPLC. The absolute configuration of **6a** was established by Kusumi's modified MTPA method using *R* and *S* MTPA esters **6c** derived from **6a**.[10]

Cyclization of **6a** with $Hg(OTf)_2$ in dichloromethane at -40°C for 8 h (the reaction was quenched by the addition of aq NaCl solution) afforded **7**, $[\alpha]_D^{17}$ +30.7° (*c* 1.0, $CHCl_3$), as a sole product in 64% yield. Thus not only the chirality but also the regio chemistry was nicely controlled by C-9 oxygen functionality during the cyclization by $Hg(OTf)_2$. Every attempt to crystallize the product **7** or its derivatives failed. Therefore the absolute configuration of the product **7** was temporary assigned according to the mechanistic consideration through the transition state **A**. When **7** was treated with $NaBH_4$ or $LiAlH_4$ in order to cleave the mercury group, an unexpected radical cyclization took place, providing a mixture of four diastereomeric products **8**.[11]



6a **7** **8**

R = $CONHCH(CH_3)C_{10}H_7$-(*S*)



6c: $\Delta\delta$ (ppm) = δ_S - δ_R

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(Received February 22, 1993)