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Synthesis of Stereotriads by Oxymercuration of Substituted Cyclopropylcarbinols

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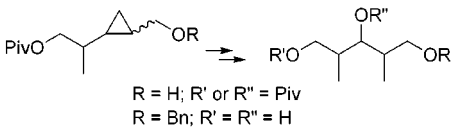
ABSTRACT



Cyclopropylcarbinol derivatives bearing an adjacent methyl-substituted stereocenter and a remote *β*-hydroxy group protected as a pivalate underwent anchimerically assisted regio- and diastereoselective oxymercurations, affording after reductive demercuration, an access to stereotriads.

Polypropionate fragments are found in a large variety of natural products of biological interest, such as polyene macrolide antibiotics (rapamycin, milbemycin), "unusual macrolides" (rutamycin), polyether ionophores (ionomycin), marine natural products (discodermolide, denticulatin), and macrocyclic lactams (rifamycin, streptovaricin).[1,2] In connection with our studies concerning the development of methods for polyketide synthesis,[3] the oxymercuration−demercuration of cyclopropylcarbinol derivatives of type **A** having a stereogenic center at C_2 (R = CH_3) and a protected hydroxy group at C_1 has been investigated, with the aim of obtaining functionalized stereotriads[4] of type **B** (Scheme 1).

Scheme 1. Oxymercuration−Demercuration of Cyclopropanes **A**

High levels of regio- and stereocontrol are usually observed in the oxymercuration of cyclopropylcarbinols.[5−7] However, when compounds of type **A** (R_1 = H or TBDPS and R = R_2 = H, *trans* diastereomers) were treated with mercuric trifluoroacetate, a complex mixture of products was obtained, but the reaction proceeded in modest yield when R_1 = $COCH_3$.[5b] Although internal participation of the ester moiety was suggested, no further evidence was provided.

In light of these results, substrates **1a**−**c**[8] were protected as pivaloic esters **2a**−**c** and subjected to oxymercuration (Figure 1).

When compounds **2a**−**c** were treated with mercuric trifluoroacetate (2 equiv, CH_2Cl_2, rt),[5b] a rapid reaction occurred, and after treatment with an aqueous solution of

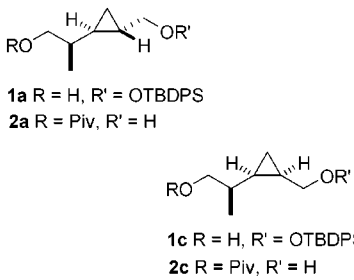


Figure 1. Cyclopropanes **1a**−**c** and **2a**−**c**.

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(2) Marchionni, C.; Vogel, P. *Helv. Chim. Acta* **2001**, *84*, 431−472 and references therein.

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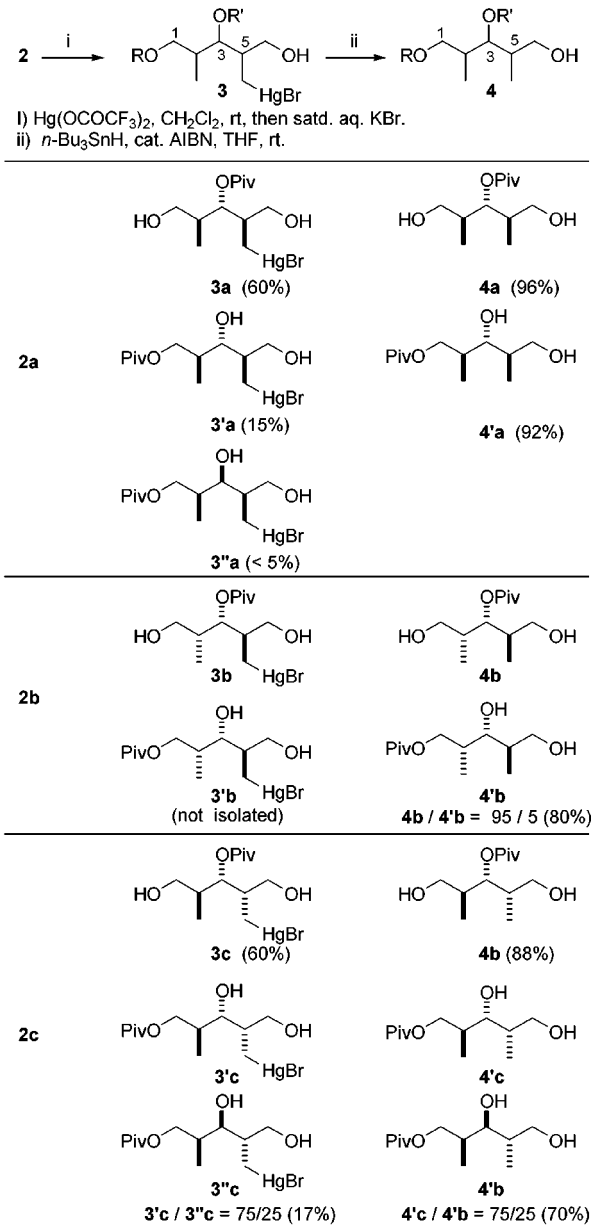
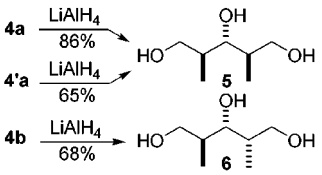
KBr, the organomercuric bromides **3** were formed, isolated, and characterized in the case of **2a** and **2c**. A reductive demercuration using *n*-Bu_3SnH and AIBN in THF[9] afforded stereotriads **4**. The results are reported in Table 1.

Table 1. Oxymercuration of Cyclopropanes **2a**−**c**



The oxymercuration of **2a** led to two separable organomercuric bromides, **3a** and **3′a**, in 60% and 15% yield, respectively. A third minor component, whose structure could not be fully elucidated, was assigned as **3″a** and was also detected in the crude reaction mixture (<5%).[10] The reductive demercuration of **3a** and **3′a** led respectively to **4a** (96%) and **4′a** (92%). These two compounds, which only differ by the positioning of the ester group, were reduced with $LiAlH_4$ and converted to the same known *anti*,*anti*-triol **5** (Scheme 2).[11] Similarly, the oxymercuration of **2b** and subsequent

Scheme 2. Correlation of Configuration for Compounds **4**



reductive demercuration afforded a regioisomeric mixture of diols **4b** and **4′b** (80% yield, 95/5 ratio).[10] The relative configuration of **4b** was unambiguously deduced after reduction with $LiAlH_4$ to the known *anti*,*syn*-triol **6** (Scheme 2).[11]

In the case of compound **2c**, the oxymercuration led to three organomercuric bromides **3c**, **3′c**, and **3″c** in a ratio of 80/15/5.[10] After purification by flash chromatography, **3c** was isolated in 60% yield and an inseparable mixture of **3′c** and **3”c** (75/25 ratio) was obtained in 17% yield. Reductive demercuration of **3c** afforded the corresponding stereotriad **4b** (88%), and the mixture of **3′c** and **3″c** was transformed to stereotriads **4′c**/**4′b** (70% yield, 75/25 ratio). From this study, it appears that the presence of an ester group, such as a pivalate, is essential to the success of these diasteroselective oxymercurations.[12] Furthermore, they proceed with inversion of configuration (= 95% diastereoselection) at the stereocenter bearing the newly introduced secondary oxygenated moiety (C_3). However, mixtures of products are obtained, due to partial migration of the ester group from the primary to the secondary hydroxyl group. A reasonable scenario involved an anchimerically assisted oxymercuration by the ester carbonyl moiety that would predominantly proceed with inversion of configuration, leading to an intermediate dioxacarbenium species, which upon hydrolysis would afford a regioisomeric mixture of the secondary and primary pivalate esters of the corresponding stereotriad (Scheme 3).

To obtain stereotriads having the two primary alcohol functions differentiated, we investigated the oxymercura-

(3) BouzBouz, S.; Popkin, M. E.; Cossy, J. *Org. Lett.* **2000**, *2*, 3449−3451.

(4) (a) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489−503. (b) Hoffman, R. W.; Dakmann, G.; Andersen, M. W. *Synthesis* **1994**, 629−638.

(5) (a) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882−6889. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094−2096.

(6) Barrett, A. G. M.; Tam, W. *J. Org. Chem.* **1997**, *62*, 4653−4664.

(7) Kocovsky, P.; Grech, J. M.; Mitchell, W. L. *J. Org. Chem.* **1995**, *60*, 1482−1483.

(8) (a) Cossy, J.; Blanchard, N.; Hamel, C.; Meyer, C. *J. Org. Chem.* **1999**, *64*, 2608−2609. (b) Cossy, J.; Blanchard, N.; Meyer, C. *Synthesis* **1999**, 1063−1075.

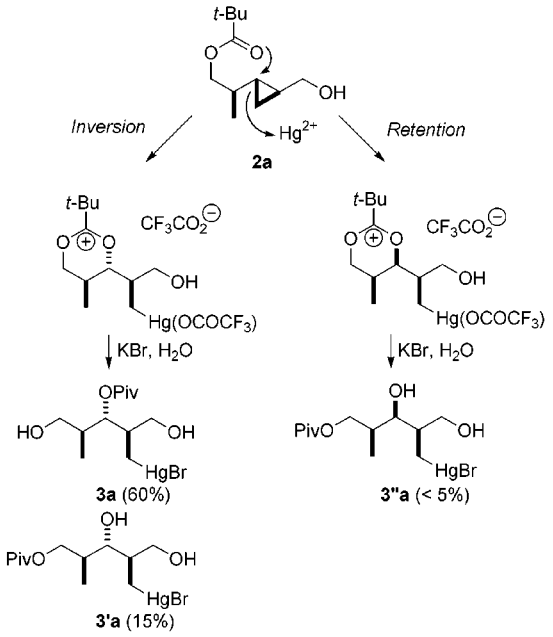
(9) Whitesides, G. M.; San Fillipo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611−6624

(10) The ratios of regio- and diastereomers have been determined by NMR.

(11) Domon, L.; Vogeleisen, F.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 2773−2776.

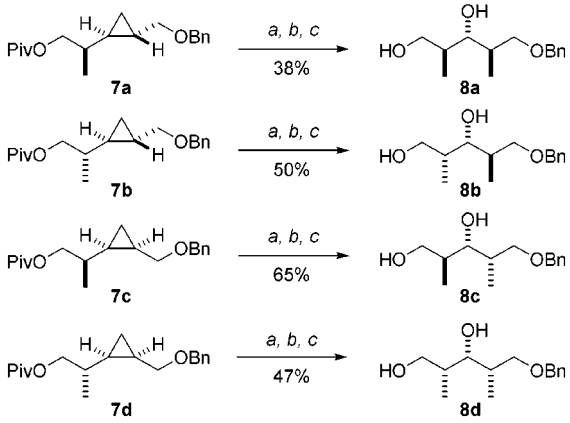
(12) No reaction was observed for substrates of type **A** (R = CH_3, R_1 = PMB, R_2 = H) bearing a *p*-methoxybenzyl protecting group.

Scheme 3. Anchimeric Assistance of the Ester Group in the Oxymercuration of **2a**



tion of the benzyl ethers **7a**−**d**. These compounds were subjected to a three-step sequence involving oxymercuration with mercuric trifluoroacetate (2 equiv, CH_2Cl_2, rt) and subsequent aqueous workup with KBr, reductive demercuration with *n*-Bu_3SnH, and deprotection of the pivalate with $LiAlH_4$. Better results were observed using this two-step reduction protocol, although $LiAlH_4$ could also initiate the reductive demercuration.[5b] The diastereomeric stereotriads **8a**−**d** were obtained in 38−65% overall yields and in a diastereoselective fashion (dr = 95/5). Their relative configurations were confirmed by comparison with the literature data,[13−15] confirming that these anchimerically assisted oxymercurations proceed with inversion of configuration (Scheme 4).

Scheme 4. Synthesis of Stereotriads[a]



[a] (a) $Hg(OCOCF_3)_2$, CH_2Cl_2, rt, then aqueous saturated KBr; (b) *n*-Bu_3SnH, catalytic AIBN, THF, rt; (c) $LiAlH_4$, THF, 0 °C.

The oxymercuration of cyclopropylcarbinol derivatives bearing a methyl-substituted adjacent stereocenter and a remote oxygenated moiety protected as an ester affords a possible route to all diastereomeric sterotriads by simply varying the relative configuration of the cyclopropane ring (*cis* or *trans*) and the *syn* or *anti* relative configuration of the adjacent stereocenter. Application of this method to natural product synthesis is currently underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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