Symmetry Breaking of Novel C_2 Chiral Across-Ring 1,3-Dienes

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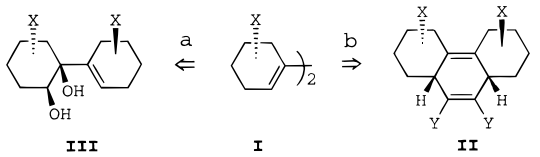
Received July 6, 1998

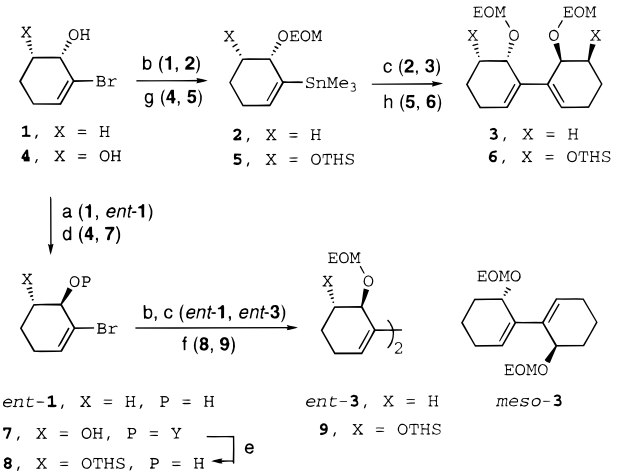
Enantiomerically pure C_2-symmetric compounds are powerful tools for chemistry.[1] Nevertheless, their use as chiral templates for the synthesis of unsymmetrical targets is only efficient provided that no additional elements or steps are required to improve the statistical results of the symmetry-breaking step.[2] Monofunctionalization has been the unique strategy described for C_2 symmetry breaking.[3,4] Up to now, the possibility of a C_2 symmetry breaking induced by a symmetry-driven functionalization at both homotopic sites remains experimentally unexplored.

We herein report on this possibility by using the formation of the unsymmetrical structures **II** as model. In this context, the Diels−Alder reaction of the hitherto unknown chiral C_2 across-ring 1,3-dienes **I**[5,6] and a $D_{\infty h}$ symmetric acetylene (Scheme 1) has been carried out. The driving force for C_2 symmetry breaking is now the conservation of the orbital symmetry[7] of a $4\pi^s + 2\pi^s$ process. In addition, dienes **I** have been transformed into the structures **III** by an osmium-catalyzed bis-hydroxylation reaction. This process[8] illustrates that monofunctionalization, as defined above, can also be applied on dienes **I** to induce C_2 symmetry breaking.

Scheme 1. C_2 Symmetry-Breaking of Dienes I by Means of a Monofunctionalization Strategy (a) and by a Symmetry-Driven Strategy (b)



Scheme 2[a]



[a] Key: (i) *p*-$NO_2C_6H_4CO_2H$ (YOH), PPh_3, DEAD, THF, rt; (ii) LiOH (1 N), THF/MeOH (2:1); (iii) $ClCH_2OEt$ (Cl-EOM), *i*-Pr_2EtN, CH_2Cl_2, −20 °C to rt; (iv) *n*-BuLi, $ClSnMe_3$, THF, −78 °C to rt; (v) $Cu(NO_3)_2$-$(OH_2)_3$, THF, rt; (vi) dimethylhexylsilyl chloride (Cl-THS), imidazole, DMF, 0 °C to rt; (a) i, ii (71%, two steps); (b) iii (93%), iv (83%); (c) v (88%); (d) i (72%); (e) vi (87%), ii (96%); (f) iii (93%), iv, v (61% two steps); (g) vi (92%), iii (95%), iv (78%); (h) v (73%).

Preparation of bis-2,2′-cyclohexenol derivative **3** was first addressed (Scheme 2). Both enantiomers of the chosen starting precursor, 2-bromo-2-cyclohexenol (**1**), can be efficiently prepared,[9] and they can be interconnected[10] by taking advantage of their chirality plane.[11] Therefore, structures **II** and **III** or their enantiomers could be synthesized from **1** or *ent*-**1**.

The protection of the allylic alcohols of **1** and *ent*-**1** as their ethoxymethoxy derivatives (EOM) followed by transmetalation (*n*-BuLi, THF, −78 °C) and subsequent treatment with trimethyltin chloride (THF, −78 °C to rt) gave, respectively, the corresponding trimethylvinylstannanes **2** and *ent*-**2** (77% from **1** and *ent*-**1**, respectively). The key homocoupling processes from each **2** and *ent*-**2** were performed by treatment with $Cu(NO_3)_2(OH_2)_3$ (THF, rt, 88%).[12,13] When the same protocol was used starting from *rac*-**1**, a mixture of *rac*-**3** and *meso*-**3** (1:1)[14] was obtained.

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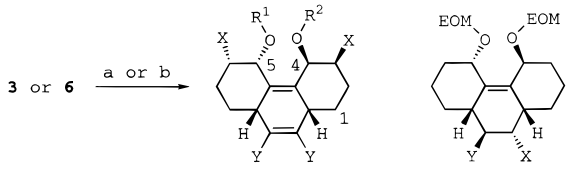
S0022-3263(98)01296-1 CCC: $15.00
Published on Web 09/05/1998

Scheme 3[a]



10 X = H, Y = CO_2Me, R^1 = R^2= EOM **14** X = OH, Y = H
11 X = OTHS, Y = CO_2Me, R^1= R^2 = EOM **15** X = Y = CN
12 X = Y = H, R^1-R^2= CH_2
13 X = OTHS, Y = H, R^1-R^2= CH_2

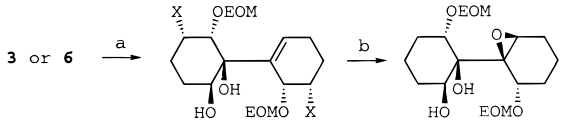
[a] Key: (a) DMAD, PhH, reflux, 86% for **10**, 97% for **11**; (b) (i) (*E*)-$NO_2CH{=}CHSO_2Ph$, reflux, (ii) *n*-Bu_3SnH, AIBN, PhMe, reflux, 70% for **12** (two steps), 73% for **13** (two steps).

The introduction of two additional oxygenated groups to the structure of diene **3** prompted us to prepare dienes **6** and **9** to facilitate eventual synthetic manipulations on the cyclohexenyl moiety. Scheme 2 shows the synthesis of diastereoisomeric dienes **6** and **9** from enantiomerically pure diol **4**.[15]

We subsequently focused on the C_2 symmetry breaking of dienes **3** and **6** induced during $4\pi^s-2\pi^s$ processes. We used two different 2π partners, dimethyl acetylenedicarboxylate (DMAD) ($D_{\infty h}$ symmetry) and a synthetic equivalent of acetylene[16] (Scheme 3). We have used the sequence Diels–Alder reaction of dienes **3** and **6** with (*E*)-1-nitro-2-(phenylsulfonyl)ethylene[17] followed by treatment of the crude mixture with tri-*n*-butyltin[18] as synthetic equivalent of acetylene. In all cases, adducts **10**–**13** (86, 97, 70, and 73% yield, respectively) were formed as unique products. The most important features[19] of the unsymmetrical structure of such products are as follows: (1) a global concave–convex shape, (2) an equatorial orientation of the substituent on C-5 (see Scheme 3 for numbering), and (3) the disposition over the convex surface of the axial substituent on C-4 (Scheme 3).

Remarkably, a complete control of the regiochemistry can be coupled whith the C_2 symmetry breaking when an appropiate dienophile is used. Thus, reaction of **3** with (a) 1-cyanovinyl acetate followed by *one-pot* reduction with excess $NaBH_4$ or with (b) fumaronitrile yielded **14** (75%) and **15** (82%), respectively, as unique products (Scheme 3).

Scheme 4[a]



X = H, **16**
X = OTHS, **17**

[a] Key: (a) 4-methylmorpholine *N*-oxide, OsO_4, acetone, H_2O, rt, 77% for **16**, 63% for **17**; (b) *t*-BuOOH, $VO(acac)_2$, PhH, rt, 70%.

On the other hand, we decided to study the C_2 symmetry-breaking process induced by the osmium-catalyzed bis-hydroxylation reaction of dienes **3** and **6**. Under standard conditions,[20] (4-methylmorpholine *N*-oxide, OsO_4, acetone, rt), diols **16** (77%) and **17** (63%) were the only products formed (Scheme 4). In this case, *proximity*, as defined by Bertz,[2a] is now active. In addition, functionalization of diols **16** and **17** as allylic alcohols allows further substrate-directable reactions. Thus, as a preliminary example, we have found that the vanadium-catalyzed epoxidation of **16** (*t*-BuOOH, $VO(acac)_2$, PhH, rt)[21] yields epoxy diol **18** (70%) (Scheme 4).

In conclusion, we have described two different strategies for the efficient C_2 symmetry breaking of enantiomerically pure novel chiral C_2 across-ring 1,3-dienes.[22] The first one, which is unprecedent, uses a symmetry-driven functionalization. The second one is based on the usual monofunctionalization strategy. A synthetic correlation between the unsymmetrical backbone of the morphinans and of the bicyclic core of zaragozic acids (squalestatins) throughout dienes **I** is currently underway as a further application of these new methods.

Acknowledgment. Financial support by DGICYT (Grant No. PB95-0065) and DGES (Grant No. PB96-0832) is acknowledged. G.G.-R. is grateful to the Ministerio de Educación y Cultura for a predoctoral fellowship. We are grateful to Dr. Gregg Whited (Genencor International, Inc.) for the generous gift of the *cis*-diol for **4** and to Drs. M. Bernabé and B. Herradón for helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for compounds **3**, *meso*-**3**, **6** and **9**–**18**. Molecular mechanics protocol and discussion. Table 1 showing the steric energy values for the conformers of **10** and **12**. Figures with a view of the most stable conformers (15 pages).

JO981296I

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