Synthesis of Highly Functionalized Diquinanes by the Regio- and Stereoselective Cleavage of Homo-Diels−Alder Cycloadducts

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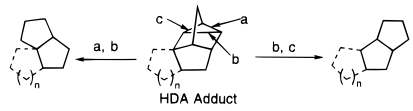
We have been investigating various aspects of the cobalt- and nickel-catalyzed homo-Diels−Alder (HDA) reaction including the regio-, stereo-, and enantioselectivity of the intermolecular cycloaddition, and we also reported the first examples of the intramolecular reaction.[1−5] Our overall objective is to demonstrate the utility of the HDA cycloaddition as a route to the synthesis of fused polycyclic natural products[6] through a sequence of cycloaddition and selective cleavage of the strained HDA cycloadduct. As shown in Scheme 1, selective cleavage of two cyclopropane bonds could lead to diquinanes or linearly or angularly fused triquinanes (if the cycloadduct was prepared via an intramolecular HDA reaction). In this paper, we report that cyclopropane cleavage by oxymercuration of 5-substituted HDA cycloadducts is highly regio- and stereoselective leading to a new route to diquinanes.

Nickon showed that cleavage of the cyclopropane in deltacyclane can be achieved under acidic conditons. Acetolysis of **I** initially formed a 1.5:1 mixture of *exo*-2-brendyl acetate **II** and *exo*-4-brexyl acetate **III**, which was converted to a 49:1 mixture after 92 h under equilibrating conditions.[7a] Protonolysis of structurally similar nortricyclene derivatives also leads to cleavage of the cyclopropane (Scheme 2).[7]

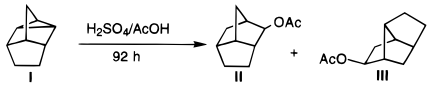
We selected mercury(II) salts rather than acid in order to examine the regio- and stereoselectivity of the opening in potentially acid sensitive, functionalized deltacyclanes. In addition, the use of mercury(II) as the electrophile rather than a proton would provide an additional site for subsequent reactions of the ring-opened products.[8−10] Mercury(II) salts are known to selectively cleave cyclopropyl carbinols and inductive effects may be responsible for the regiochemistry observed.[9,10] We anticipated that an analogously positioned 5-oxy substituent in the HDA adducts would also influence the regioselectivity of the cyclopropane cleavage,[11] with the stereoselectivity being controlled by the rigid polycyclic framework.

The required 5-substituted deltacyclanes **1a**−**e** were prepared via a nickel-catalyzed HDA reaction of 7-substituted norbornadienes and phenyl vinyl sulfone,[1b] followed by removal of the sulfone moiety with sodium amalgam.[12,13] Oxymercuration could then lead to as many as 24 cyclopropane ring-opened products, since any one of the three cyclopropane bonds could

Scheme 1



Scheme 2



be cleaved and each bond cleavage option has two pairs of regio- and stereoisomers.

The results of our initial studies on the oxymercuration of 5-substituted deltacyclanes confirm that the reaction is regio- and stereoselective, as shown in Table 1. A variety of different 5-substituted HDA adducts (a *tert*-butyl ether, a silyl ether, a methyl ether, a benzyl ether, and even a phenyl ring) undergo oxymercuration with mercury(II) trifluoroacetate followed by reduction with $LiAlH_4$ to provide *anti-exo*-8-substituted brendan-2-ols **3a**−**e** in good yield. Selective cleavage of the C_2-C_3 bond in the deltacyclanes was observed. The cyclopropane bond that is *syn* to the electron-withdrawing OR group is more nucleophilic and therefore more prone to attack by the electrophilic mercury.[14] These reactions were also highly stereoselective with respect to the incoming nucleophile giving *exo* attack exclusively. The regio- and stereochemistry of adduct **3a** were confirmed by X-ray crystallography on an ester derivative and the structures of **3b**−**e** were confirmed by converting **3a** to **3b**−**e** and comparing their NMR spectra.[15] These ring-opened products were shown to have the same regio- and stereochemistry as **3a**. The reactivity was clearly influenced by the 5-substituent, as demonstrated by the complex mixture of products formed when the parent adduct (Y = H) or an

(1) For a recent review on metal mediated cycloaddition reactions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) (a) Lautens, M.; Edwards, L. G. *J. Org. Chem.* **1991**, *56*, 3762. (b) Lautens, M.; Tam, W.; Edwards, L. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2143. (c) Lautens, M.; Edwards, L. G.; Tam, W.; Lough, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10276.

(3) (a) Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 5627. (b) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.

(4) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8.

(5) For other representative examples of metal-catalyzed homo-Diels−Alder reactions, see: (a) Schrauzer, G. N.; Eichler, S. *Chem. Ber.* **1962**, *95*, 2764. (b) Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3239. (c) Noyori, R.; Umeda, I.; Kawauchi, H.; Takaya, H. *J. Am. Chem. Soc.* **1975**, *97*, 812. (d) Lyons, J. E.; Myers, H. K.; Schneider, A. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 273. (e) Lautens, M.; Crudden, C. M. *Organometallics* **1989**, *8*, 2733. (f) Lautens, M.; Edwards, L. G. *Tetrahedron Lett.* **1989**, *30*, 6813. (g) Brunner, H.; Muschiol, M.; Prester, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 652. (h) Duan, I. F.; Cheng, C. H.; Shaw, J. S.; Cheng, S. S.; Liou, K. F. *J. Chem. Soc., Chem. Commun.* **1991**, 1347. (i) Buono, G.; Pardigon, O. *Tetrahedron: Asymmetry* **1993**, *4*, 1977.

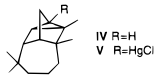
(6) For reviews on cyclopentanoid synthesis, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *82*, 141. (c) Ramaiah, M. *Synthesis* **1984**, 529.

(7) For examples of acid-catalyzed cleavage of the cyclopropane in deltacyclane and nortricyclene derivatives, see: (a) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; Digiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904. (b) Nickon, A.; Hammons, J. H. *J. Am. Chem. Soc.* **1964**, *86*, 3322. (c) Hammons, J. H.; Probasco, E. K.; Sanders, L. A.; Whalen, E. J. *J. Org. Chem.* **1968**, *33*, 4493. (d) Werstiuk, N. H.; Cappelli, F. P. *Can. J. Chem.* **1980**, *58*, 1725.

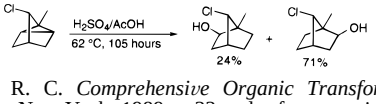
(8) For reviews of cyclopropane cleavage methods, see: (a) Preston, P. M.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627. (b) DePuy, C. H. *Top. Curr. Chem.* **1973**, *40*, 73. (c) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605. (d) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (e) Rappoport, Z., Ed.; *The Chemistry of the Cyclopropyl Group*; J. Wiley and Sons: London, 1987; Parts 1 and 2.

(9) For examples of mercury-induced ring opening of cyclopropanes, see: (a) Lukina, R.; Gladshetein, M. *Dokl. Akad. Nauk SSSR* **1950**, *71*, 65. (b) DePuy, C. H.; MsGuirk, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 2366. (c) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (d) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094. (e) Lambert, J. B.; Chelius, E. C.; Bible, R. H., Jr.; Hajdu, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331. (f) Kocovsky, P.; Srogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* **1994**, *116*, 186. (g) Kocovsky, P.; Grech, J. M.; Mitchell, W. *J. Org. Chem.* **1995**, *60*, 1482. (h) Landais, Y.; Parra-Rapado, L. *Tetrahedron Lett.* **1996**, *37*, 1209.

(10) Reaction of longicyclene **IV** with $Hg(OAc)_2$ is reported to result in initial cyclopropane cleavage and subsequent ring closure via 1,3-elimination of AcOH. Addition of NaCl provides **V** (Suryawanshi, S. N.; Nayak, U. R. *Ind. J. Chem.* **1980**, *19B*, 5). The presence of the methyl group on the cyclopropane may be responsible for this unusal behavior.



(11) Werstiuk[7d] reported a modestly regioselective and highly chemoselective cleavage of 7-chloro-1-methylnortricyclene under acidic conditions.



(12) Larock, R. C. *Comprehensive Organic Transformation*; VCH Publishers, Inc.: New York, 1989; p 33 and references cited therein.

(13) For other methods of desulfonylation including SmI_2/THF/−78 °C or Mg/EtOH, respectively, see: Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. Lee, G. H.; Choi, E. B.; Lee, E.; Pak, C. S. *Tetrahedron Lett.* **1993**, *28*, 4541.

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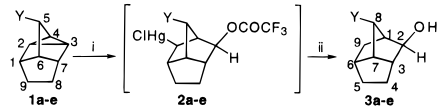
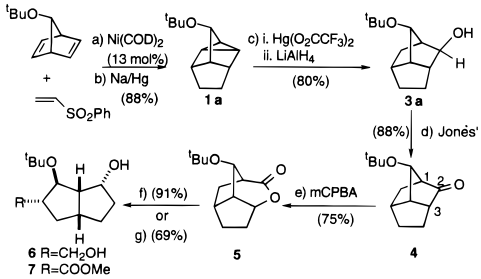
Table 1. Oxymercuration of 5-Substituted Deltacyclanes



Entry	Y	Product	Isolated Yield	Entry	Y	Product	Isolated Yield
1	O^{t}Bu	**3a**	80%	5	Ph	**3e**	80%
2	OTIPS	**3b**	78%	6	H	**3f/f'**	20% [a]
3	OMe	**3c**	70%	7	n-hexyl	---	---- [b]
4	OBn	**3d**	66%				

[a] A 4:1 mixture of an *exo*-brendan-2-ol and *exo*-brexan-4-ol was obtained accompanied by several other products. [b] A complex mixture of products was observed by TLC.

Scheme 3[a]



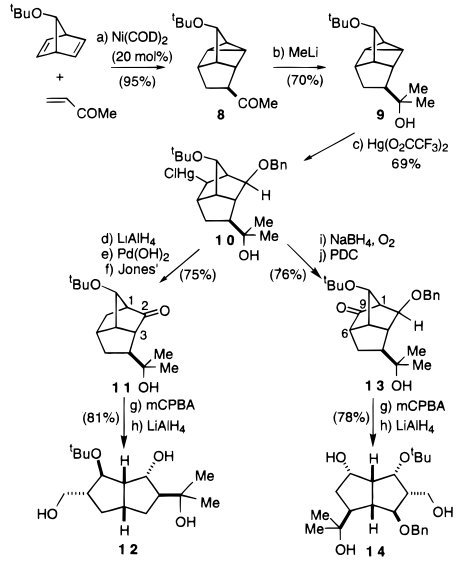
[a] Key: PPh_3 (26 mol %), $ClCH_2CH_2Cl$, 80 °; (b) Na_2HPO_4, MeOH, rt; (c) (i) CH_2Cl_2, rt, 24 h, NaCl, (ii) THF, 0 °C; (d) acetone; (e) cat. *p*-TsOH, CH_2Cl_2, reflux; (f) $LiAlH_4$, THF, 0 °C; (g) $BF_3{\cdot}OEt_2$, MeOH.

alkyl-substituted derivative (Y = *n*-hexyl) is treated with $Hg(O_2CCF_3)_2$.[16]

Following oxidation of the alcohol to a ketone, Baeyer−Villiger oxidation with mCPBA (*meta*-chloroperoxybenzoic acid) was highly regioselective with insertion of oxygen occurring exclusively at the C_2-C_3 bond in the brendanone **4**, Scheme 3.[17,18] The structure of lactone **5** was confirmed by ^{1}H NMR decoupling and NOE experiments. Reductive cleavage of the lactone with $LiAlH_4$ or transesterification with $BF_3{\cdot}Et_2O$ in dry MeOH afforded functionalized diquinanes **6** and **7** in good yields.

The potential of this methodology in the synthesis of more highly functionalized diquinanes is illustrated in Scheme 4. Nickel-catalyzed HDA reaction of 7-*tert*-butoxynorbonadiene with methyl vinyl ketone was regio- and stereoselective and led to the *anti-exo*-HDA cycloadduct **8** in 95% yield.[1b] Conversion of **8** to the tertiary alcohol **9** by addition of MeLi was followed by a regio-and stereoselective oxymercuration with mercury(II) trifluoroacetate in the presence of benzyl alcohol to give **10** in 69% yield. Demercuration of **10** with $LiAlH_4$, removal of the benzyl group by hydrogenolysis, and oxidation of the resulting alcohol cleanly afforded ketone **11** (75%, three steps). In analogy to our previous results, Baeyer−Villiger oxidation of ketone **11** with mCPBA occurred exclusively on the C_2-C_3 bond, giving diquinane **12** in excellent yield after $LiAlH_4$ reduction of the lactone formed from the Baeyer−Villiger oxidation.[19]

Scheme 4[a]



[a] Key: (a) PPh_3 (40 mol %), $ClCH_2CH_2Cl$, rt, 18 h; (b) THF, −78 °C; (c) $Hg(O_2CCF_3)_2$ (2 equiv), BnOH (10 equiv), CH_2Cl_2, rt, 36 h, then NaCl; (d) THF, 0 °C; (e) cyclohexene, EtOH, reflux; (f) acetone; (g) cat. *p*-TsOH, CH_2Cl_2, reflux; (h) THF, 0 °C; (i) EtOH; (j) CH_2Cl_2.

On the other hand, when the organomercurial **10** was reacted with $NaBH_4$ in the presence of O_2, a mixture of the *exo* and *endo* alcohols was produced which was oxidized to a single ketone (**13**) upon treatment with PDC (pyridinium dichromate). Baeyer−Villiger oxidation of ketone **13** with mCPBA occurred exclusively on the C_6-C_9 bond to give one regioisomeric lactone[20] which was subsequently reductively cleaved to diquinane **14**.[19] This sequence produces highly functionalized diquinanes with complete control of six or seven stereogenic centers in seven to eight steps.

These examples illustrate the potential of a sequence involving a transition metal-catalyzed HDA cycloaddition−selective cleavage strategy in the synthesis of substituted diquinanes. Our ongoing studies are focused on the synthesis of triquinanes by several variations of this overall strategy. Details of these studies will follow shortly.

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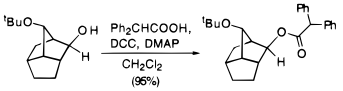
Supporting Information Available: Experimental procedures and compound characterization data for all new compounds (18 pages). See any current masthead page for ordering and Internet access instructions. JA962223O

(14) The stereochemistry of the carbon bearing the HgCl group has not been determined.

(15) We were unable to prove the stereochemistry of **3a** by various chemical and spectroscopic techniques. We therefore determined the structure of the corresponding 2,2-diphenyl acetate derivative by X-ray analysis. Details of the X-ray analysis have been submitted for publication to *Acta Crystallogr, Sect. C*.

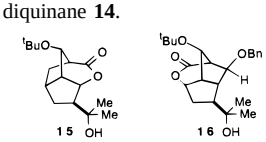


(16) We have found mercuration in the presence of a nucleophile, such as methanol, benzyl alcohol, *tert*-butyl hydroperoxide, or water, is also very efficient.

(17) For reviews on the Baeyer−Villiger oxidation, see: (a) Krow, G. R. *Org. React.* **1993**, *43*, 251. (b) Hassall, C. H. *Org. React.* **1957**, *9*, 73.

(18) For a similar example of a regioselective Baeyer−Villiger oxidation of brendanone, see: Heumann, A.; Kaldy, S.; Tenaglia, A. *J. Chem. Soc., Chem. Commun.* **1993**, 420.

(19) The stereochemistry of lactone **15**, resulting from Baeyer−Villiger oxidation of **11** was determined by ^{1}H NMR decoupling and NOE studies as described in the Supporting Information. The stereochemistry of lactone **16**, resulting from oxidation of **13**, was deduced from ^{1}H NMR decoupling and NOE studies of diquinane **14**.



(20) As expected, the presence of the benzyl ether did not influence the regioselectivity of the Baeyer−Villiger reaction since the carbon β to the electron-withdrawing benzyloxy group is not the carbon undergoing migration. However, in adduct **17** (R = TIPS (triisopropylsilyl)), the regioselectivity of the Baeyer−Villiger reaction is reduced to 2:1. When R = Ms (methanesulfonyl), the regioselectivity is actually reversed. Further work on the effect of β-substituents in directing the Baeyer−Villiger reaction will be reported in due course.