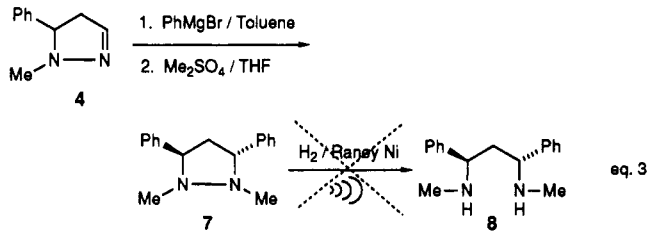
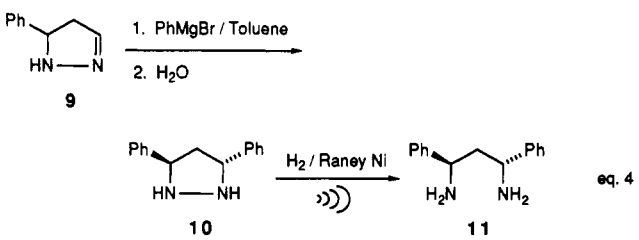


However, the tetrasubstituted nature of the hydrazine functionality prevented all our attempts to cleave the N–N bond and to obtain the desired diamine 8.

Another approach to the diamine 8 was more successful. Indeed, although less reactive than 4, pyrazoline 9 reacted with PhMgBr in toluene, at 100 °C, for 1 h. Hydrolysis of the reaction mixture gave the unstable pyrazolidine 10 which was cleaved under our recently described conditions[6] (assistance by ultrasound) to yield the pure *d,l* primary diamine 11 in 74% overall yield (eq 4). This diamine was recently obtained and transformed to diamine 8 by Denmark[12] following a similar reaction scheme but using the



pyrazoline 9, protected as the *N*-Boc derivative, and $PhCeCl_2$ instead of PhMgBr.

With these new reaction conditions, we believe that the hydrazone functionality will become a viable alternative to imines which are commonly preferred, due to their higher reactivity.

Supplementary Material Available: Experimental procedures and ^1H and ^{13}C NMR spectra of adducts **3a–h**, pyrazoline **6**, and pyrazolidine **7** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The ^1H NMR data of the two diastereomers of 7 are described: Elguero, J.; Marzin, C.; Tizané, J. *Tetrahedron Lett.* **1969**, 513.

(12) Denmark, S. E.; Kim, J.-H. *Synthesis* **1992**, 229.

Regioselective Ring Opening of Cyclopropane by Mercury(II) and Transmetalation of the Intermediate Organomercurial with Lithium and Copper Reagents. A Novel, Stereoselective Approach to Cyclobutanes†

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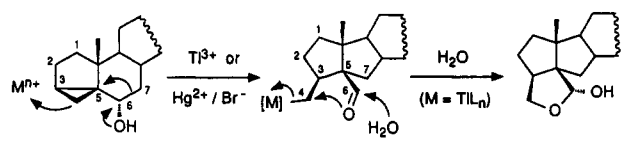
Summary: Cleavage of cyclopropyl derivative 1 by means of Hg^{2+} occurs with a skeletal rearrangement to afford a stable organomercurial 3 which on treatment with Me_2CuLi gives cyclobutanol 9; analogous conjugate addition is also reported (**10** → **15**).

Stereo- and regioselective cleavage of cyclopropanes[1,2] by means of electrophilic metal complexes can serve as an attractive strategy for the construction of up to three contiguous chiral centers.[3]

Recently, we have described a stereospecific, thallium(III)-mediated cleavage of steroidal cyclopropane derivative 1 which triggered a unique skeletal rearrangement affording lactol 4 via the thalliated intermediate 2 (Scheme I).[6] Mercury(II) ion, isoelectronic with Tl(III), is also known to be capable of cleavage of a cyclopropane.[1,5,7] Since organomercurials are generally more stable than their organothallium counterparts, it was of great interest to explore the reactivity of 1 toward Hg(II), aiming at isolation of the organomercurial product and exploration of its reactivity, including transmetalation.

3α,5-Cyclo-5α-cholestan-6α-ol (1)[8] was treated with $Hg(NO_3)_2 \cdot H_2O$ in DME/MeCN (2:5) at rt. The reaction was monitored by TLC, and when the starting material

Scheme I



could no longer be detected (ca. 1.5 h), aqueous KBr was added.[9] The mixture was worked up to afford organo-

† Dedicated to Professor John E. McMurry on the occasion of his 50th birthday.

(1) (a) Rappoport, Z., Ed. *The Chemistry of the Cyclopropyl Group*; J. Wiley and Sons: London, 1987. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

(2) Cyclopropanes themselves can be synthesized with high diastereo- and enantioselectivity.[1]

(3) Two mechanisms can be discerned for the ring opening of cyclopropanes, namely the *edge* (favored by reagents capable of back donation, such as transition metals[1] and halogens[4]) and the *corner* cleavage (typical for electrophiles that are incapable of back donation, e.g., H^+, Hg^{2+}, and Tl^{3+}).[5,6]

(4) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156.

(5) (a) Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 2988; *J. Org. Chem.* **1989**, *54*, 1383. (b) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1990**, *55*, 4136. (c) Lambert, J. B.; Chelius, E. C.; Bible, R. H., Jr.; Hajdu, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331.

(6) Kočovský, P.; Pour, M.; Gogoll, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* **1990**, *112*, 6735.

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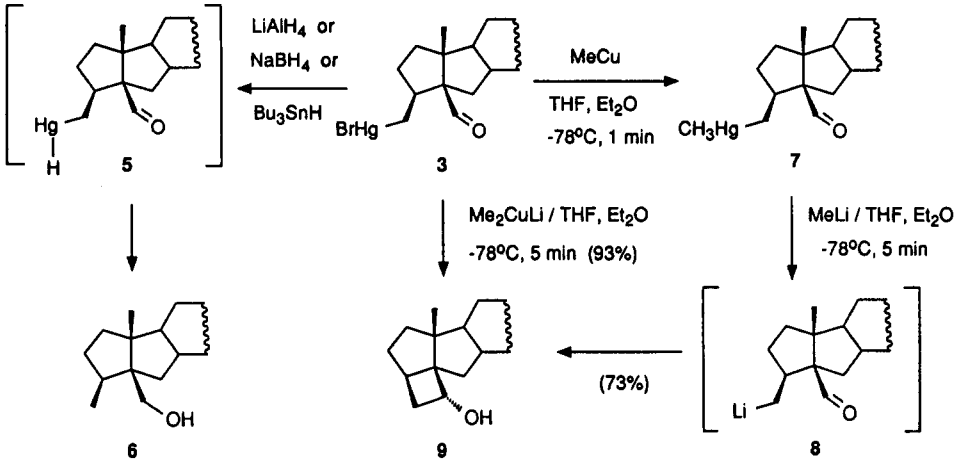
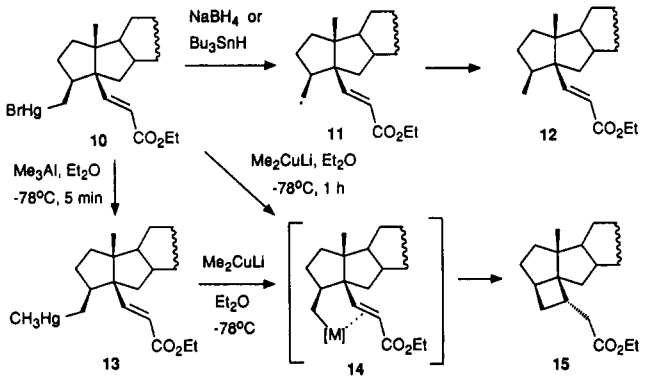
Scheme II



mercurial **3** in 97% isolated yield.[10,14,15] Unlike the thalliated species **2**, compound **3** was fairly stable and could be purified by chromatography and crystallized.

Reduction of **3** with a variety of hydride reagents furnished demercurated alcohol **6** in a quantitative yield (Scheme II). Since Bu_3SnH also gave **6** (1 min at 0 °C), we assume the generation of mercury hydride **5** as an intermediate followed by an intramolecular reduction of the aldehyde group. No cyclobutane ring closure was observed.[16]

Scheme III



In order to achieve an intramolecular addition to the aldehyde group, we have attempted a transmetalation of **1** that would generate a more reactive organometallic species. Since MeLi produced a complex mixture, we turned our attention to intermediates derived from softer metals, such as copper.[20] Rather surprisingly, MeCu (generated by mixing equal parts of CuI and MeLi) effected clean methylation on mercury, providing the MeHg derivative **7** (94%).[21,22] Treatment of **7** with MeLi at low temperature resulted in the formation of the desired cyclobutanol **9**.[23] Alternatively, we have found that **9** can be obtained in one pot on reaction of **3** with Me_2CuLi.[24]

Having successfully accomplished intramolecular addition of an intermediate organometallic species to the C=O bond to produce a 4-membered ring (**3** → **9**), we set out to explore the intramolecular conjugate addition reaction of this or related intermediates to an activated C=C bond. To our delight, aldehyde **3** readily afforded the required α,β-unsaturated ester **10**[25] on Horner–Emmons

(7) (a) Collum, D. B.; Mohamadi, F.; Hallock, J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094. (c) Rood, I. D. C.; Klump, G. W. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 303. (d) Langbein, G.; Siemann, H.; Gruner, I.; Müller, C. *Tetrahedron* **1986**, *42*, 937. (e) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192. (f) For review on organomercurials, see: Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985.

(8) Wagner, A. F.; Wallis, E. S. *J. Am. Chem. Soc.* **1950**, *72*, 1047.

(9) Much slower reaction was observed with $(CF_3CO_2)_2Hg$; $(AcO)_2Hg$ did not react at rt at all. The DME/MeCN mixture was found out to be superior to dioxane, which, in turn, was the solvent of choice for the Tl(III)-mediated cleavage.[6]

(10) The structure was determined by NMR spectra using H,H-COSY,[11] HMQC,[12] HMBC,[12] and selective INEPT.[13] ^1H NMR: 9.72 (s, 1 H, CHO); ^{13}C NMR: 34.78 ($-CH_2HgBr$), 206.22 (–CHO); ^{199}Hg NMR: −1063 ppm. The full assignment of carbon signals in the ^{13}C NMR spectrum has been achieved.

(11) Bax, A.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 164.

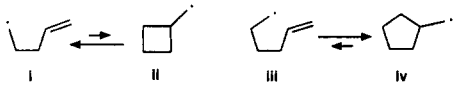
(12) (a) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285. (b) Cavanagh, J.; Hunter, C. A.; Jones, D. N. M.; Keeler, J.; Sanders, J. K. M. *Magn. Reson. Chem.* **1988**, *26*, 867.

(13) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.

(14) In the absence of the 6α-hydroxy group, the reaction with Hg^{2+} occurs via a simple ring-opening followed by elimination to give the corresponding allylic acetate: Blossey, E. C. *Steroids* **1969**, *14*, 725. For review on the chemistry of cyclopropano-steroids, see: Evans, J. M.; Kasal, A. *Acta Cient. Venez.* **1972**, *23*, 95.

(15) Other isoelectronic cations (Au^+ and Pb^{4+}) and those of high redox potential as well as other ions (Ce^{4+}, Cu^+, Cu^{2+}, Ag^+, and Mn^{3+}) were found either to be inert or to convert **1** to cholesterol or its esters (acetate, nitrate, etc.).

(16) Radicals of the type **i** do not cyclize to **ii**, as the equilibrium is shifted toward the open species **i**.[17] In contrast, five-membered rings can readily be formed by the intramolecular radical addition (**iii** → **iv**).[17-19]



(17) For discussion, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; p 143.

(18) Imanishi, T.; Ohra, T.; Sugiyama, K.; Ueda, Y.; Takemoto, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 269.

(19) Although C=O is not particularly prone to radical addition, successful cyclizations producing 6-membered rings via an intramolecular radical addition have been described: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116 and 8102. (b) Tsang, R.; Dickson, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. Samarium(II) seems to be an excellent promoter of this type of reaction: (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(20) Bergbreiter, D. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 4937.

(21) This result itself may represent a new method for the preparation of dialkyl mercury derivatives RHgR′ from the readily available organomercury halides RHgBr. Other reagents that also gave high yields of **7** were Me_3Al, Me_2Zn, and Me_2Mn.

(22) ^1H NMR: 0.32 (s, CH_3Hg), 9.81 (s, CH=O) ppm. ^{13}C NMR: 20.94 (CH_3Hg), 207.37 (CH=O) ppm. ^{199}Hg NMR: −161.6 ppm; *m/z* 600 (M^+).

(23) IR: ν_{OH} = 3430 and 3600 cm^{-1}; ^1H NMR: 4.19 (dd, 1 H, J = 4.6 and 5.4 Hz, C*H*OH) ppm; ^{13}C NMR 68.59 (d) ppm. The structure of **9** was corroborated by oxidation which afforded the corresponding cyclobutanone which had mp: 112–114 °C. $[\alpha]_D$: −9° (*c* 2.4). IR: 1750 cm^{-1}. ^1H NMR: 2.61 (dd, 1 H, J = 17.6 and 6.8 Hz, 4β-H), 2.90 (dd, 1 H, J = 17.6 and 8.6 Hz, 4α-H) ppm. ^{13}C NMR 212.93 (C=O) ppm.

(24) This reaction can be understood in terms of the Lipshutz observation of an equilibrium between a cuprate and alkyllithium (2 Me_2CuLi ⇌ MeLi + Me_3Cu_2Li): Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

olefination.[26] Attempted radical cyclization of **10**, using $NaBH_4$ or Bu_3SnH (Scheme III), gave only the reduced product **12** (in 81% and 87% yield, respectively).[27,28] However, as with the aldehyde **3**, copper reagents proved more rewarding. First, organomercurial **10** was methylated with MeCu or Me_3Al to give **13** (in 91% and 95% yield, respectively.)[29] Although in this instance MeLi produced a complex mixture on reaction with **13**, Me_2CuLi afforded the desired cyclobutane derivative **15** (40%).[30] Alternatively, **15** was obtained in much higher isolated yield (75%) in one pot from **10** on reaction with Me_2CuLi.[31] This behavior suggests that the actual reactive species **14** involves copper. Although the structure of **14** is unknown, it seems reasonable to assume[20] that M = $CuLiCH_3$ or $CuHgLiCH_3$ and that the more suitably positioned C(4) in the complex **14** adds across the double bond in preference to the CH_3 group.

In conclusion, we have achieved a unique, regio- and stereoselective opening of a cyclopropane ring by Hg(II) followed by a skeletal rearrangement, generating a "5,5" system (**1** → **3**). As a result of specific transmetalations (with Li or Cu) we have been able to effect a highly stereoselective, intramolecular addition to a carbonyl group and/or across a conjugated double bond, and so construct a "5,5,4" tricyclic system (**3** → **9** and **10** → **15**). These transformations represent a novel methodology for cyclobutane annulation that may be of general use in view of the rather limited number of alternative approaches[32] and of the failure of radical reactions.[33] Alternatively, we believe that the strategy employing organomercurials, which can be generated by a number of stereoselective routes,[7f] may result in the development of a general method for the stereoselective construction of rings of various size, and for intermolecular coupling as well.

Acknowledgment. We thank Profs. M. Nilsson and J.-E. Bäckvall, and Dr. T. Olsson for stimulating discussions and Drs. G. Griffith and A. Gogoll for obtaining the NMR spectra. We also thank Merck Sharp and Dohme and the University of Leicester for financial support to J.Š.

Supplementary Material Available: Representative experimental procedures and characterization data for new compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(25) IR: $\nu_{C=O}$ = 1702 cm^{-1}. ^1H NMR: 5.92 (d, J = 16.0 Hz, 1 H, CH=C*H*CO_2Et), 7.06 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 119.57 (d), 151.98 (d), 166.46 (s) ppm.

(26) Although the reaction was rather slow [$(EtO)_2P(O)CH_2CO_2Et$, BuLi, THF, reflux for 12 h] due to steric hindrance, the yield of **10** was very good (73%). To our knowledge, this is the first successful Wittig-type olefination in the presence of an HgBr group in the substrate molecule. No reaction of aldehyde **3** was observed with Wittig reagents Ph_3P=CHR or with Ph_3As=CH_2, presumably due to the preferential coordination of Hg to P or As.

(27) Analogous radical cyclization of an organomercurial intermediate has been successfully employed to construct a five-membered ring.[18]

(28) Attempted intramolecular Heck coupling, using various Pd(II)-reagents, resulted solely in β-elimination (to give a product with an endocyclic double bond in 93% yield). This is in sharp contrast to the analogous cyclization that occurs readily to produce five-membered rings.[18]

(29) ^1H NMR: 0.25 (s, 3 H, CH_3Hg), 5.84 (d, 1 H, J = 16.0 Hz, CH=C*H*CO_2Et), 7.15 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 20.92 (CH_3Hg), 118.03 (d), 154.73 (d), 166.89 (s) ppm.

(30) IR: $\nu_{C=O}$ = 1728 cm^{-1}. ^{13}C NMR: 173.20 (s) ppm.

(31) Cyclobutane derivative **15** can also be obtained in high yield (92%) from **13** on reaction with Me_3Al/BuLi. We believe that, in this instance, the Lewis acid (Me_3Al) accelerates the conjugate addition, as in its absence only a complex mixture was produced.

(32) For methods of construction of four-membered rings, see: (a) Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 843; Vol. 3, pp 588 and 620; Vol. 5, pp 63, 123, and 899. (b) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. 1, pp 39, 96, and 145. For a recent enantioselective approach, see: (c) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.

(33) Recently, an ionic, intramolecular addition across a conjugated double bond to form a four-membered ring, has been reported: Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495.

Novel, Enantioselective Lactone Construction. First Synthesis of Methylenolactocin, Antitumor Antibiotic from *Penicillium* sp.

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Summary: The first synthesis of (−)-methylenolactocin, which illustrates a novel approach to enantiopure γ-butyrolactones and serves to confirm the structure and establish the absolute stereochemistry of the natural product, is reported.

α-Methylene-γ-butyrolactones,[1] ubiquitous, biologically significant compounds, represent approximately 10% of all structurally elucidated natural products.[1e] Enantioselective entry to the γ-butyrolactones, the structural units from which the α-methylene analogues are generally derived,[1b,e,f] is thus methodologically important and has, in recent years, been addressed with varying degrees of success in a number of laboratories.[2]

(1) For reviews on the occurrence, biological properties, and synthesis of α-methylene-γ-butyrolactones, see: (a) Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo, 1973. (b) Grieco, P. A. *Synthesis* **1975**, 67–82. (c) Heywood, H.; Harborne, J. B.; Turner, B. L. *The Biology and Chemistry of the Compositae*; Academic Press: London, 1977; Vols. 1 and 2. (d) Fischer, N. H.; Oliver, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2. (e) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94–110. (f) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157–183.

(2) For recent approaches, see: Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255–256. Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482. Toda, F.; Tanaka, K.; Omata, T.; Nakamura, K.; Oshima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5151–5152. Marino, J. P.; Perez, A. D. *Ibid.* **1984**, *106*, 7643–7644. Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211–213. Thijs, L.; Waanders, P. P.; Stokkingreef, E. H. M.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 332–337. Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 966–968. Salaun, J.; Karkour, B. *Tetrahedron Lett.* **1988**, *29*, 1537–1540. Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69–71. Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981–1984. Ohkuma, T.; Kitamura, M.; Noyori, R. *Ibid.* **1990**, *31*, 5509–5512. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Ibid.* **1991**, *32*, 4163–4166. Doyle, M. P.; van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982–8984.

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