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Enantioselective Synthesis of 2-Substituted Cyclobutanones

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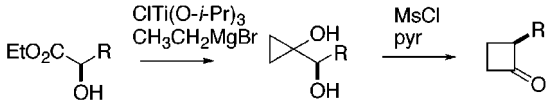
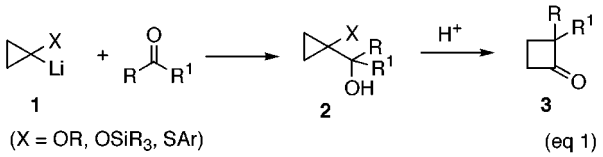
ABSTRACT

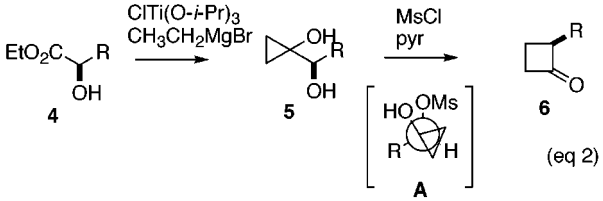


An enantioselective synthesis of 2-substituted cyclobutanones has been achieved by sequential application of the titanium-mediated cyclopropanation of α-hydroxy esters and the pinacol-type rearrangement of the resulting α-hydroxycyclopropylcarbinols.

Cyclopropanes and cyclobutanes offer considerable utility as useful building blocks in organic synthesis.[1] Their unique reactivity associated with the strain release upon cleavage of these small rings has found many elegant applications in the development of new annulation methods for five-membered, six-membered, and medium-sized rings. The synthetic utility of these strained molecules is enhanced by the presence of a carbonyl group. For example, cyclobutanones, in particular, 2-alkenylcyclobutanones, have been utilized in some imaginative ring expansion reactions.[1d,2] Although several methods for preparing cyclobutanones and cyclobutanes are available, their enantioselective syntheses have received relatively little attention.[2,3] A paucity of general procedures for preparing enantiomerically pure cyclobutane derivatives remains in striking contrast with recent impressive advances in asymmetric cyclopropanation. Herein we report an enantioselective synthesis of 2-substituted cyclobutanones by facile rearrangement of α-hydroxycyclopropylcarbinols.

Among the known methods for preparing cyclobutanones (which can also be extended to the synthesis of 2-alkenylcyclobutanones),[4] a commonly used approach utilizes the heteroatom-substituted cyclopropylcarbinyl−cyclobutyl ring expansion, **2** → **3** (eq 1), where the heteroatom substituent





X of **2** not only facilitates the rearrangement but also affords the ketone functionality of **3** upon hydrolysis. The requisite starting materials **2** are obtained by addition of a suitable cyclopropyllithium reagent **1** to carbonyl compounds (including enones and enals). An alternative route (eq 2) involving α-hydroxycyclopropylcarbinols **5** (i.e., X = OH in **2**), which should be easily prepared by the Kulinkovich

(1) For general reviews, see: (a) Battiste, M. A.; Coxon, J. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Chapter 6. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (d) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F.. *Top. Curr. Chem.* **1986**, *133*, 83. (e) Salaün, J. R. In *Small Ring Compounds in Organic Synthesis III*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 1988; pp 1−71.

(2) For an excellent review, see: Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797.

(3) Recently Krief and co-workers reported the pinacol rearrangement of α-hydroxycyclopropylcarbinols: (a) Krief, A.; Ronvaux, A.; Tuch, A. *Tetrahedron* **1998**, *54*, 6903. See also: (b) Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504. Fukumoto and co-workers also developed an asymmetric variant of Trost's rearrangement of oxaspiropentanes to cyclobutanones by means of the Sharpless asymmetric epoxidation of cyclopropylidene alcohols: (c) Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863 and references therein. For other related studies, see: (d) Hiroi, H.; Nakamura, H.; Anzai, T. *J. Am. Chem. Soc.* **1987**, *109*, 1249. (e) Salaun, J.; Karkour, B.; Ollivier, J. *Tetrahedron* **1989**, *45*, 3151. (f) Ollivier, J.; Legros, J.-Y.; Fiaud, J.-C.; de Meijere, A.; Salaün, J. *Tetrahedron Lett.* **1990**, *31*, 4135.

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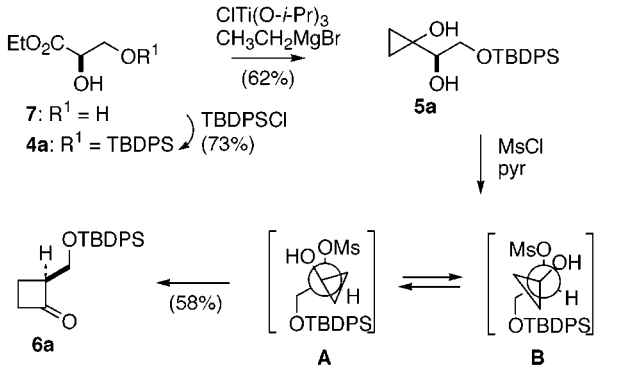
cyclopropanation[5,6] of α-hydroxy esters **4**, would lend itself to an enantioselective synthesis of 2-substituted cyclobutanones **6**, since enantiomerically pure **4** are readily available by standard methods. Preferential migration of a single diastereotopic C−C bond of cyclopropanol **5**, along with inversion of configuration at the stereocenter, is obligatory to achieve high enantioselectivity.[3a,b]

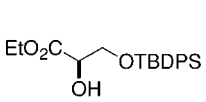
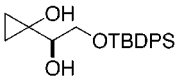
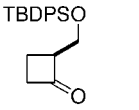
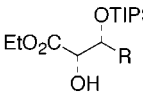
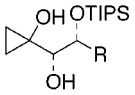
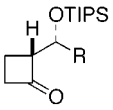
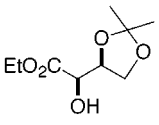
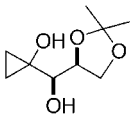
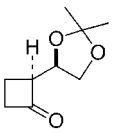
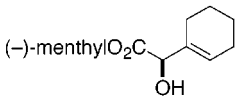
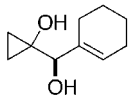
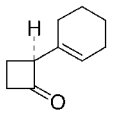
Sharpless asymmetric dihydroxylation of acrylates provides easy access to the starting α-hydroxy esters.[7] Thus, the known diol **7** (77−80% ee) was subjected to selective silylation of the primary alcohol to afford **4a** in 73% yield (Scheme 1). The Kulinkovich cyclopropanation of **4a** with

Scheme 1



the ethyl Grignard reagent afforded directly the requisite substrate **5a**, albeit in moderate (62%) yield. Although a higher overall yield can be obtained by protection of the free hydroxyl group prior to the Kulinkovich cyclopropanation, the direct conversion of **4a** to **5a** was chosen for convenience in the present work. Treatment of **5a** with mesyl chloride in pyridine resulted in facile pinacol rearrangement to afford **6a**, $[\alpha]^{25}_D = -19.3°$ (*c* 0.4, CH_2Cl_2), in 58% (unoptimized) yield (Table 1). Since the optical rotation of **6a** is known,[8] a comparison of the optical rotation values {lit.[8a] $[\alpha]^{25}_D =$ $-16.2°$ (*c* 1.0, CH_2Cl_2); lit.[8b] $[\alpha]^{25}_D = -22.5$ to $-24.1°$ (*c* 2.0, $CHCl_3$)} allowed us to ascertain that the key rearrangement of **5a** → **6a** takes place with a high (>90%) level of chirality transfer. The (*S*) configuration of cyclobutanone **6a** can be rationalized by the antiperiplanar requirement in the preferred transition state arising from conformer **A**. As shown in the Newman projection, the alternate transition state from conformer **B** suffers from nonbonded interactions between the cyclopropyl ring protons and the substituent CH_2-OTBDPS.[9]

Table 1

starting esters	α-hydroxycyclopropylcarbinols	cyclobutanones
 **4a**	 **5a** 62%	 **6a** 58%
 **4b**: R = Me	 **5b**: R = Me 56%	 **6b** 57%
4c: R = $(CH_2)_6CH_3$	**5c**: R = $(CH_2)_6CH_3$ 43%	**6c** 67%
4d: R = $(CH_2)_3OTHP$	**5d**: R = $(CH_2)_3OTHP$ 49%	**6d** 57%
 **4e**	 **5e** 41%	 **6e** 71% 10 : 1
 **4f**	 **5f** 43%	 **6f** 72%

(4) See, inter alia: 1. addition of vinylketenes to olefins: (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (b) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330. 2. epoxidation of alkylidenecyclopropanes: (c) Salaun, J. R.; Champion, J.; Conia, J. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 320. (d) Cohen, T.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 27. 3. α-arylthio- or alkoxycyclopropylcarbinol-to-cyclobutanone rearrangement: (e) Trost, B. M.; Keeley, D. E.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 3068. (f) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088. (g) Cohen, T.; Matz, J. R. *Tetrahedron Lett.* **1981**, *22*, 2455. (h) Wenkert, E.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 2030. (i) Krumpolc, M.; Rocek, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 114 and references therein.

(5) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts-kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts-kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66.

(6) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.

(7) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(8) (a) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471. (b) Sato, M.; Ohuchi, H.; Abe, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 313.

(9) The origin of the high stereoselectivity is reminiscent of Julia's stereoselective synthesis of trisubstituted olefins by acid-promoted rearrangement of cyclopropylcarbinols: Julia, M.; Julia, S.; Tchen, S.-Y. *Bull. Soc. Chim. Fr.* **1961**, 1849.

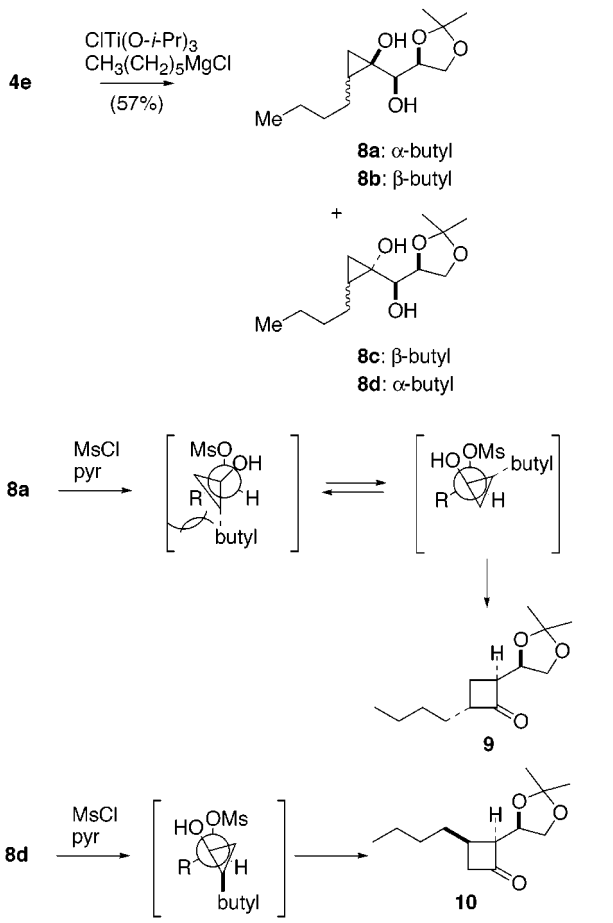
To facilitate analysis of the degree of chirality transfer in the rearrangement process, α-hydroxycyclopropylcarbinols **5** bearing an adjacent stereocenter were next examined, where the diastereoselectivity of the cyclobutanone formation can be easily determined by the ^1H NMR analysis. Following the identical reaction sequence, **4b** and **5b** were prepared uneventfully starting from ethyl *trans*-crotonate.[10] Ring expansion of **5b** by the action of MsCl gave, as a single

isomer, cyclobutanone **6b** (57% yield), the stereochemistry of which was assigned by analogy to that of **5a** → **6a**. Treatment of **5b** with Martin sulfurane also afforded **6b** in 77% yield.[11] In both of the ring expansion reactions effected by MsCl and Martin sulfurane, the observed stereochemical outcome is congruent with the concerted rearrangement as generalized in transition state **A** but precludes the intermediacy of the corresponding oxaspiropentane. Ring expansion of the related oxaspiropentanes was shown by Fukumoto[3c,12] to proceed with inversion of configuration at the migrating terminus: the rearrangement of the oxaspiropentane derived from **5a** would thus lead to the enantiomer of **6a**.

As shown in additional examples in Table 1, the ring expansion reactions of α-hydroxycyclopropylcarbinols **5c**−**f** were also found to take place with excellent selectivity. Particularly noteworthy is a convenient preparation of synthetically useful 2-alkenylcyclobutanone **6f**, which relies on the successful cyclopropanation of allylic alcohol **4f** without complication due to formation of an allylic titanium intermediate.[13]

Preparation of trisubstituted cyclopropanols by treatment of **4e** with hexylmagnesium chloride in place of ethylmagnesium bromide under otherwise identical Kulinkovich cyclopropanation conditions [i.e., in the presence of ClTi(O-*i*-Pr)$_3$] surprisingly afforded all four possible diastereomers **8** (57%) as a 1:0.7:0.3:0.25 mixture (Scheme 2).[14] Difficulties in separating the individual isomers have so far precluded a detailed investigation of the subsequent pinacol rearrangement of **8a**−**d**. However, cursory examination with a diastereomeric mixture of **8** revealed that steric effects in the transition state outweigh the migratory aptitude of the two alkyl substituents, leading to 2,3-disubstituted or 2,4-disubstituted cyclobutanones. It is presumed that ring expansion of two diastereomers **8a**,**d** will occur with the indicated stereochemistry given in Scheme 2.[15]

Scheme 2



In summary, sequential application of the titanium-mediated cyclopropanation of readily available α-hydroxy esters and the pinacol-type rearrangement of the resulting α-hydroxycyclopropylcarbinols provides convenient access to enantiomerically pure 2-substituted cyclobutanones.[16,17] The latter ring expansion reaction was found to proceed with an excellent degree of stereoselectivity.

Acknowledgment. We thank the National Science Foundation (CHE98-13975) for financial support. We also thank a referee for bringing to our attention ref 3a.

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(10) Silylation of the diols derived from osmylation of *β*-alkyl acrylates was found to proceed with regioselective protection of the *β*-alcohol: Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012.

(11) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

(12) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.

(13) Under the Kulinkovich reaction conditions, allylic alcohols and ethers could give the corresponding allylic titanium reagents. The successful formation of **5f** is a consequence of unfavorable exchange between the parent, the unsubstituted titanacyclopropane, and the trisubstituted olefin of **4f**, which in turn reflects the greater stability of the former presumed intermediate. For related work, see: (a) refs 6a,b. (b) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (c) Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916.

(14) The Kulinkovich cyclopropanation reactions of carboxylic esters bearing α-oxy or *β*-oxy substituents have been found to afford a diastereomeric mixture of *cis*- and *trans*-1,2-disubstituted cyclopropanols, in sharp contrast to the otherwise exceptional (>30:1) diastereoselectivity for the *cis* isomers: Lee, C.-W.; Cho, S. Y.; Cha, J. K. Unpublished results.

(15) In fact, Trost reported migration of the less substituted carbon in the pinacol rearrangement of 1-phenylthiocyclopropanes closely related to **8a**, although a different rationalization was advanced: Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1983**, *48*, 1131.

(16) **Representative procedure for the preparation of 6a:** To a solution of **5a** (39 mg, 0.1 mmol) in pyridine (1 mL) was added dropwise at room temperature mesyl chloride (0.085 mL, 1 mmol). The reaction mixture was stirred for 1 h, poured to ice water, and extracted three times with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel) afforded 21.4 mg (58%) of **6a** as a colorless oil.

(17) Swern oxidation of **5** affords 2-alkyl-2-hydroxycyclobutanones, as a consequence of the α-ketol rearrangement. For example, a 2:1 diastereomeric mixture of α-hydroxycyclobutanones was obtained by Swern oxidation of **5b**.