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Cross-Coupling of Cyclopropanols: Concise Syntheses of Indolizidine 223AB and Congeners

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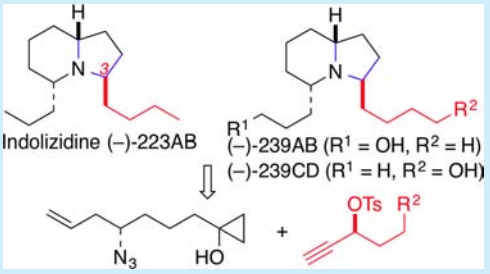
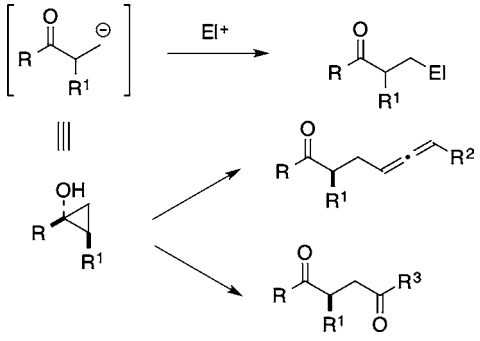
Supporting Information

ABSTRACT: A new synthetic method for indolizidine or pyrrolizidine alkaloids based on readily available and attractively functionalized cyclopropanols, as exemplified in concise syntheses of indolizidine (−)-223AB, its 3-epimer, (−)-indolizidine 239AB, and (−)-indolizidine 239CD, is reported. This work highlights the applications of S_N2' alkylation and *C*-acylation of cyclopropanols to meet stereochemical challenges in natural product synthesis. Also included is diastereoselective cyclization of the resulting aminoallene adduct for bicyclic ring formation.

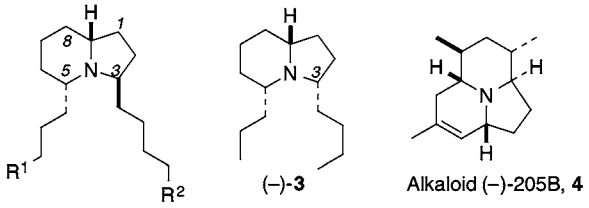


Part of our research program was directed at the development of a general synthetic method for indolizidine and pyrrolizidine alkaloids with particular emphasis on efficiency and selectivity. A cyclopropanol was viewed as a versatile platform to devise a conceptually new approach to bioactive alkaloids. Toward this end, we recently reported new ring opening reactions of cyclopropanols for C−C bond formation: (1) S_N2' alkylation and (2) *C*-acylation.[1,2] These convenient cross-coupling methods represent alkylation and acylation of cyclopropanols as a homoenolate equivalent (Scheme 1); keto homoenolates offer the greater advantage than ester homoenolates in rapid assembly of two large segments.

Scheme 1. Homoenolate Alkylation and Acylation



As an initial foray into applications in natural product synthesis, amphibian alkaloids were chosen as our first target. Many of them are characterized by the presence of two alkyl substituents at the C3 and C5 positions, as exemplified by indolizidine (−)-223AB, **1**, indolizidine (−)-239AB, **2a**, indolizidine (−)-239CD, **2b**, and alkaloid (−)-205B, **4**.[3−12] There have been no complete pharmacological studies of **1**, **3**, and other congeners, probably due to their scarcity.[13] Total synthesis enables detailed evaluation of these otherwise unavailable alkaloids, as well as structure−activity relationship studies.



Indolizidine (−)-223AB, **1** (R^1 = R^2 = H)
Indolizidine (−)-239AB, **2a** (R^1 = OH, R^2 = H)
Indolizidine (−)-239CD, **2b** (R^1 = H, R^2 = OH)

Indolizidine (−)-223AB (**1**) has been a popular target for total synthesis: 4 racemic and 10 enantioselective syntheses have been documented.[4,5] Fourteen previous syntheses notwithstanding, only two were diastereoselective and relied on S_N2 reactions for the construction of two C−N bonds.[5b,k] The remaining syntheses suffered from the conspicuous lack of diastereoselectivity. Previous syntheses clearly point to unique challenges posed by the juxtaposition of the C3 and C5 stereocenters of **1** despite its deceptively simple structure. In contrast, the stereochemical array in its unnatural C3-epimer **3** is readily amenable to diastereocontrol. Thus, **1** presents an excellent testing ground for new synthetic methods with respect to brevity, selectivity, and generality. Starting from a common cyclopropanol substrate, we herein describe concise syntheses of not only **1**, **2a**, and **2b**, but also **3**, that are divergent at a late stage.

As outlined in our retrosynthetic analysis (Scheme 2), a concise synthesis of **3** would be materialized by double

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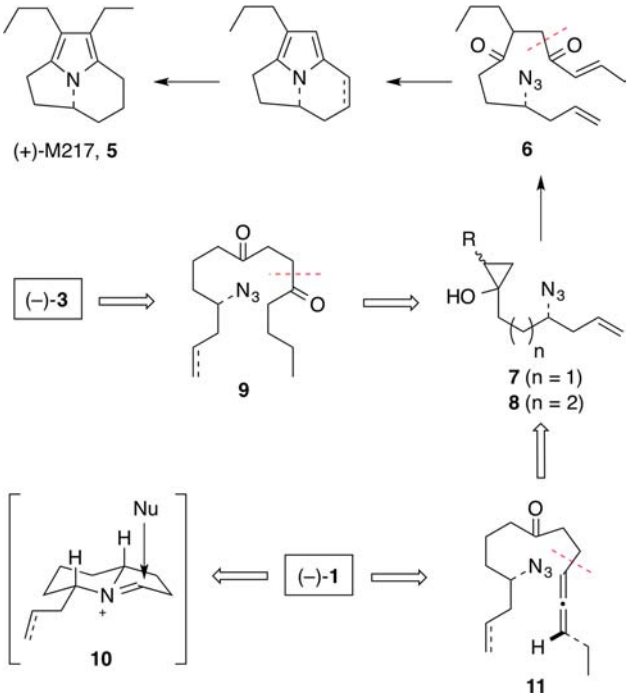
Scheme 2. Retrosynthetic Analysis of (−)-1 and (−)-3

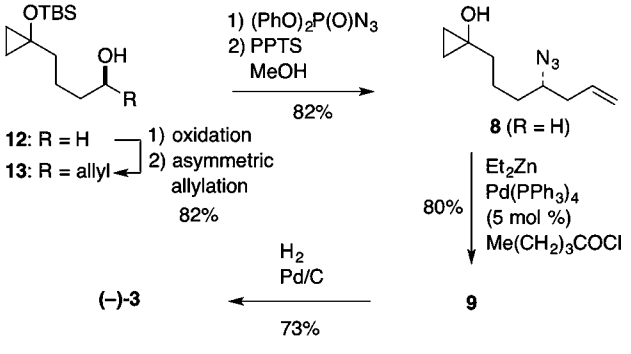


reductive amination[14] of **9** to complement our recent synthesis of (+)-myrmicarin 217, **5**,[2] by an intramolecular Paal−Knorr synthesis of **6**. The azido (or amino)-tethered 1,4-ketone **9** would be available from cross-coupling of **8** with pentanoyl chloride.

On the other hand, **1** poses a unique challenge in stereocontrol. One possible route could involve addition of the butyl side chain to iminium ion **10**. However, this method was deemed to be unattractive, as cross-coupling would entail the installation of a one-carbon unit. An attractive solution was found in an electrophilic allene cyclization.[15] The key *anti*-S_N2' alkylation of cyclopropanol **8** would offer unique and rapid access to the requisite allene intermediate. Despite recent advances in gold-catalyzed hydroamination and other useful reactions of allenes,[16] there are surprisingly only a few applications in alkaloid synthesis, and known examples are limited primarily to monocyclic ring formation.[17]

Our synthesis of (−)-**3** commenced with the cyclopropanol **12**, which had been prepared as part of studies on the Kulinkovich cyclopropanation of esters and lactones (Scheme 3).[18,19] Dess−Martin oxidation of alcohol **12** and subsequent

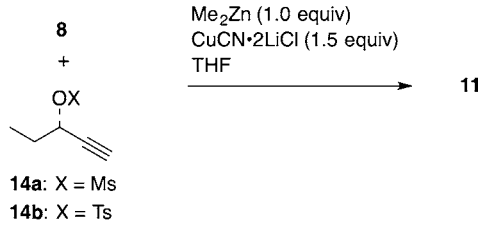
Scheme 3. Preparation of 1,4-Diketone 9 and Total Synthesis of (−)-3



asymmetric allylation by Keck's method [using (*S*)-BINOL)][20] afforded homoallylic alcohol **13** in 82% yield. Azide **8** was next prepared in 82% yield by clean displacement of the secondary alcohol of **13** with diphenylphosphoryl azide, followed by desilylation. The key cross-coupling reaction of **8** with pentanoyl chloride afforded **9** in 80% yield. Hydrogenation of **9** under standard conditions gave (−)-**3** as a single isomer in 73% yield; spectroscopic data were in excellent agreement with the literature data.[9,10] Thus, *C*-acylation of cyclopropanol **8** delivered new and concise access to **3**.

As noted in our retrosynthetic analysis, electrophilic cyclization of allene **11** was selected to achieve a concise and stereoselective synthesis of **1**. The S_N2' alkylation reaction between cyclopropanol **8** and the mesylate **14a** of the known (3*S*)-1-pentyne-3-ol[21] afforded **11** only in low yield, along with large amounts of unreacted **8**. Systematic optimization studies were undertaken for the cross-coupling reaction of *terminal* propargylic alcohol derivatives. After considerable experimentation, the following reaction parameters were found to be critically important: (1) dimethylzinc (in place of diethylzinc) for the requisite generation of the zinc cyclopropoxide; (2) tosylates in place of mesylates; (3) rt instead of low temperatures (Table 1). It should be pointed out that a large

Table 1. Cross-Coupling of 8 and 14



entry	sulfonate (equiv)	temp (°C)	products (%) **11** + unreacted **8**	
1	**14a** (3.0)	−30 to 0	12	50
2	**14b** (2.0)	−30 to 0	35	30
3	**14b** (3.0)	0	54	25
4	**14b** (2.0)	rt	80	
5	**14b** (1.5)	rt	79	

majority of the reactions involving mixed zinc/copper reagents in the literature were run at low temperatures.[22] Under optimized conditions, the desired allene **11** was obtained in 79−80% yield to set the stage of the final steps.

With **11** in hand, initial formation of imine **15** by aza-Witting reaction and subsequent reduction of the latter by $NaBH_4$ gave piperidine **16** in 82% yield (Scheme 4). Silver nitrate-mediated cyclization of aminoallene **16** proceeded cleanly to deliver **17** having the *E*-double bond configuration (J = 15.2 Hz) in 85% yield and with >20:1 selectivity.[23] Attempts for catalytic hydrogenation of **17** only yielded decomposition, presumably due to competing hydrogenolysis of the allylic C−N bond. A concise synthesis of (−)-**1** was completed by diimide reduction of two double bonds in **17**.[24] Spectroscopic data and optical rotation of (−)-**1** were in excellent accord with the literature values.[4,5] Alkaloid 223AB (**1**) was clearly distinguishable from **3** by TLC and GC/MS, as well as spectral data.

We also probed the dominant factor for stereocontrol of the key electrophilic cyclization of **16** by preparing the aminoallene epimeric to **16** starting from *ent*-**14b**. The stereoselective cyclization of each aminoallene antipode was observed and

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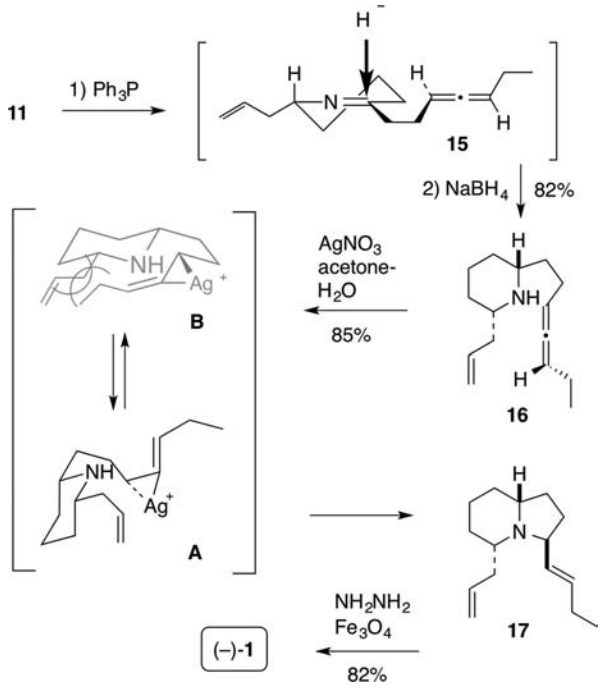
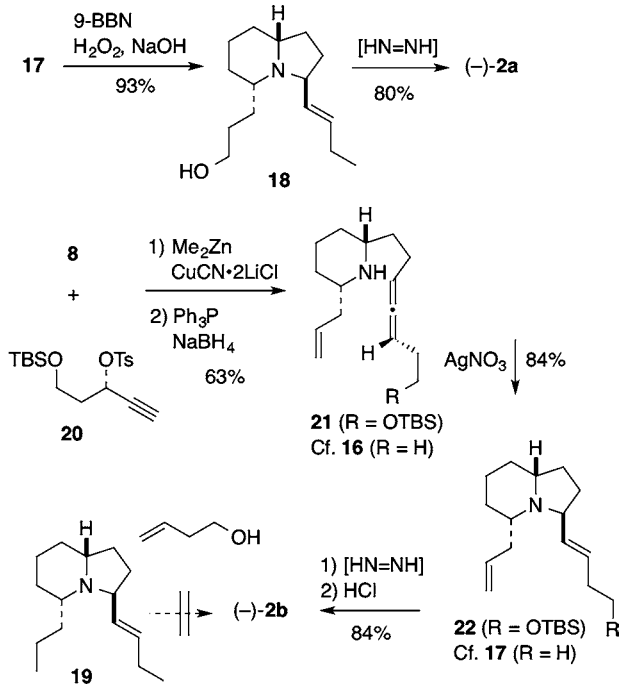
Scheme 4. Total Synthesis of (−)-1



Scheme 5. Total Synthesis of (−)-2a and (−)-2b



attributed to exceptional chirality relay from the tethered allene.[23] We believe this approach offers a general method for preparing *trans*- and *cis*-2,5-disubstituted pyrrolidines by means of an exceptional level of chirality transfer from an allene pendant.

Indolizidine **17**, the final precursor to (−)-**1**, could serve as a common intermediate for total synthesis of its hydroxylated natural products, (−)-**2a** and (−)-**2b** by straightforward elaboration of the double bonds. Indeed, chemoselective hydroboration of **17**, followed by diimide reduction of the remaining double bond of **18**, afforded a concise entry to (−)-**2a** (Scheme 5).[7] Following selective reduction of the monosubstituted olefin of **17**, cross-metathesis of the resulting allylic amine **19** with 3-buten-1-ol by the action of the Grubbs or Grubbs−Hoveyda catalysts was explored, but to no avail. Not surprisingly, **19** was recovered unreacted. By adaptation of the aforementioned synthetic sequence for (−)-**1**, an enantioselective synthesis of (−)-**2b** was achieved to demonstrate the generality of S_N2' alkylation of cyclopropanols: the use of (*S*)-tosylate **20**[25] led to a five-step synthesis of (−)-**2b**.[8]

In conclusion, we report a concise and divergent synthesis of indolizidine (−)-223AB, **1**, and (−)-**3** that showcases the utility of two cross-coupling reactions, S_N2' alkylation and *C*-acylation, of attractively functionalized cyclopropanols. A highlight is the simplicity and brevity of the synthetic sequence for **1** and **3** involving four and two steps, respectively, from the cyclopropanol **8** as a common intermediate.

These new synthetic methods entail expedient coupling of two segments and promise to be of general utility in the enantioselective syntheses of not only pyrrole, indolizidine, and pyrrolizidine alkaloids but also other natural products containing aza and oxygen heterocycles

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Das, P. P.; Belmore, K.; Cha, J. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9517.

(2) Parida, B. B.; Das, P. P.; Niocel, M.; Cha, J. K. *Org. Lett.* **2013**, *15*, 1780.

(3) Isolation of **1**: Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242.

(4) Syntheses of (±)-**1**: (a) McDonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (c) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043. (d) Edwards, O. E.; Greaves, A. M.; Sy, W.-W. *Can. J. Chem.* **1988**, *66*, 1163.

(5) Enantioselective syntheses of (−)-**1**: (a) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515. (b) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990. (c) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178. (d) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429. (e) Célimène, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457. (f) Takahat, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797. (g) Momose, T.; Toshima, M.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, *9*, 1315. (h) Kirihara, M.; Nishio,

dx.doi.org/10.1021/ol503136s | *Org. Lett.* 2014, 16, 6208−6211

T.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron* **1999**, *55*, 2911. (i) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. (j) Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169. (k) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493. (l) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. (m) Conchon, E.; Gelas-Mialhe, Y.; Remuson, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1253. (+)-**1**: (n) Gartner, M.; Weihofen, R.; Helmchen, G. *Chem.—Eur. J.* **2011**, *17*, 7605.

(6) Isolation of (−)-indolizidine 239AB (**2a**) and 239ACD (**2b**): Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265.

(7) Syntheses of (−)-indolizidine 239AB (**2a**): (a) Reference 5c. (b) Reference 5d. (c) Reddy, C. R.; Latha, B.; Rao, N. N. *Tetrahedron* **2012**, *68*, 145.

(8) For syntheses of indolizidine 239CD (**2b**), see: (a) (−)-: ref 5c. (b) (±)-: Clark, R. B.; Pearson, W. H. *Org. Lett.* **1999**, *1*, 349.

(9) Syntheses of (±)-**3**: (a) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403. (b) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. Nakagawa, Y.; Stevens, R. V. *J. Org. Chem.* **1988**, *53*, 1871.

(10) Syntheses of (−)-**3**: (a) Reference 5m. (b) Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 9621. (c) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (d) Liu, H.; Su, D.; Cheng, G.; Xu, J.; Wang, X.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1899.

(11) Isolation of **4**: Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643.

(12) Syntheses of (+)-**4**: (a) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3808. Syntheses of (−)-**4**: (b) Smith, A. B.; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247. Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. (c) Tsukanov, S. V.; Comins, D. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8626. (d) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237.

(13) Interestingly, both **1** and its unnatural C3-epimer **3** were noted to be equally potent blockers of the nicotinic acetylcholine receptor (nAChR) channel involved in the neuromuscular transmission; ref 9b.

(14) Although double-reductive amination of 1,4-dicarbonyl compounds was employed for formation of monocyclic pyrrolizidines, there are few intramolecular variants: (a) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175. (b) Boga, C.; Manescalchi, F.; Savoia, D. *Tetrahedron* **1994**, *50*, 4709. (c) Williams, I.; Kariuki, B. M.; Reeves, K.; Cox, L. R. *Org. Lett.* **2006**, *8*, 4389.

(15) Diastereoselective cyclization of δ-aminoallenes was showcased in our previous synthesis of quinolizidine alkaloids, wherein the ingrained steric bias was overridden: Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012.

(16) Muñoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164 and references therein.

(17) (a) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997. (b) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729. (c) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114. (d) Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3549. (e) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253.

(18) Esposito, A.; Taddei, M. *J. Org. Chem.* **2000**, *65*, 9245.

(19) For reviews,see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (c) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1.

(20) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **2004**, *10*, 632.

(21) (3*S*)-1-Pentyne-3-ol was prepared by adaptation of the literature procedures: (a) Chun, J.; Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **2002**, *43*, 8043. (b) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (c) Schubert, T.; Hummel, W.; Kula, M.-R.; Müller, M. *Eur. J. Org. Chem.* **2001**, 4181. (d) Arai, N.; Satoh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. *Org. Lett.* **2013**, *15*, 3030.

(22) (a) Yamamoto, Y.; Tanaka, M.; Ibuka, T.; Chounan, Y. *J. Org. Chem.* **1992**, *57*, 1024. (b) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. (c) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627. (d) Dieter, R. K.; Chen, N.; Gore, V. K. *J. Org. Chem.* **2006**, *71*, 8755.

(23) High diastereoselectivity for S_N2' alkylation reactions of cyclopropanol **8** with each antipodal tosylate (i.e., **14b** and *ent*-**14b**) indicates high (>95) ee's of all reactants; see the Supporting Information.

(24) (a) Kim, E.; Kim, S.; Kim, B. M. *Bull. Korean Chem. Soc.* **2011**, *32*, 3183. See also: (b) Pasto, D. J.; Taylor, R. T. *Org. Reactions* **1991**, *40*, 91.

(25) Prepared from the known (*S*)-diol: (a) Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 10792. (b) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 3145.