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Stereoselective Synthesis of *Cis*-Fused Chlorinated Bicyclic Ethers via CAN-Mediated Ring-Opening of Cyclopropyl Sulfides

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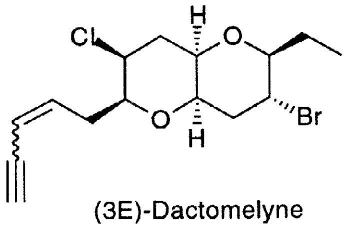
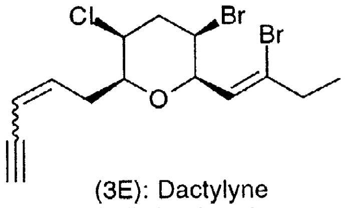
Abstract: A facile method for synthesizing 3β-chlorinated 2,6-disubstituted tetrahydropyrans is described. Introduction of a chloride to 2β-substituted and 2β,4α-disubstituted 3-oxabicyclo[3.1.0]hexyl phenyl sulfides proceeded efficiently by a CAN-mediated oxidation to give 3β-chlorinated tetrahydropyrans stereoselectively and in good yields, while the CAN-oxidation of 2β,4β-disubstituted 3-oxabicyclo[3.1.0]hexyl phenyl sulfide afforded the 3β-chlorinated tetrahydropyran as a minor product. However, by tuning the aryl group of the sulfide, the desired 2β,3β,6β-chlorinated product was obtained in good yield. The following silane-reduction of the bicyclic chlorinated acetal gave the cis-fused chlorinated bicyclic ether, where all substituents are oriented on the same side. © 1998 Elsevier Science Ltd. All rights reserved.

An important group of marine natural products is a series of nonterpenoid C15-metabolites that are derived from fatty acid metabolism.[1] The structural diversity of this kind of molecule is very wide, but all have in common polysubstituted cyclic ethers and halogen atoms with a defined stereochemistry in the side-chains and rings. Since these naturally occurring organohalogen compounds have been recognized as new medical leads,[2] several elegant methods have been developed for introducing the halogen atoms in the ring system with the aim toward total synthesis of these compounds.[3] However, there are few reliable synthetic methods for preparing these halides regio- and stereoselectively, especially in the case of sterically hindered halides. This is well demonstrated by an unsuccessful attempt for the synthesis of dactomelynes by Kozikowski.[4] Recently, Lee et al. have succeeded in constructing the substructure **C** (Scheme 1, n = 2) in the first total synthesis of dactomelynes[5] by using a two-step procedure: radical-mediated cyclization into a dichlorinated adduct and stereoselective radical dehalogenation to a β-chlorinated product.

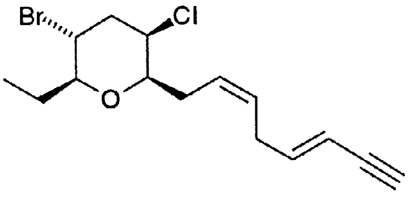
We have reported the use of cyclopropyl sulfides as a latent β-hydroxyketone moiety resulting in the stereoselective formation of monocyclic and spirocyclic ethers.[6] The key point of this reaction is the perfectly stereocontrolled nucleophilic substitution of the most substituted cyclopropyl bond by an alcohol with an inversion of configuration. In connection with our continuing studies on new synthetic methods based on the



(3E)-Dactomelyne
(3Z)-Dactomelyne



(3E): Dactylyne
(3Z): Isodactylyne



Srilankenyne

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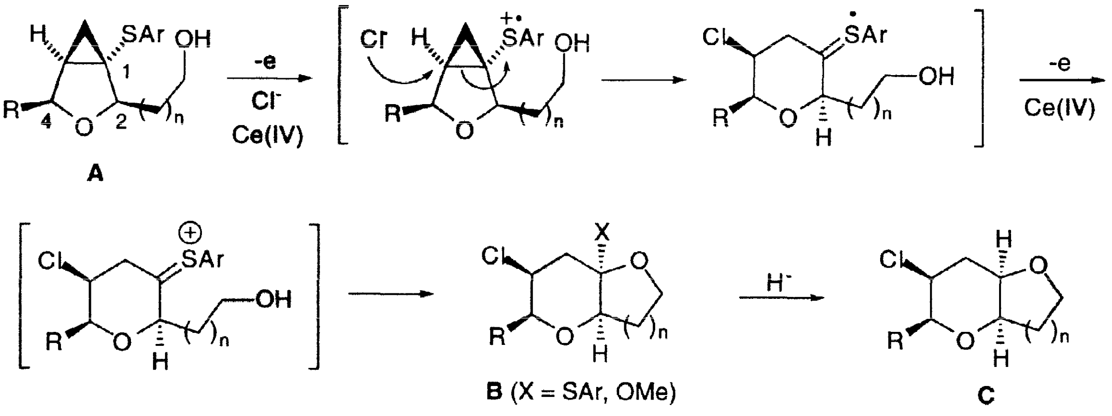
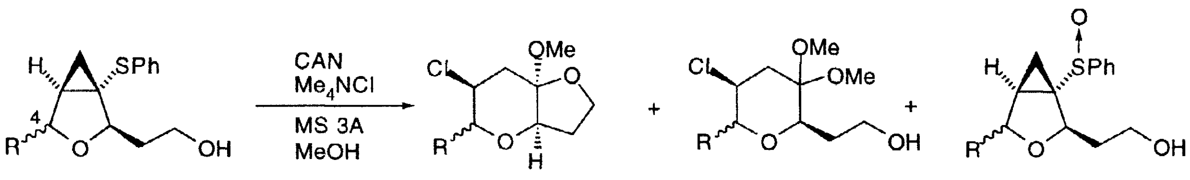


Scheme 1

CAN [ceric(IV) ammonium nitrate]-mediated ring-opening of cyclopropyl sulfides,[6,7] we are interested in the synthesis of such bicyclic ethers with a sterically hindered chlorine **C**. Our synthetic strategy is depicted in Scheme 1. If a chloride anion would attack the most substituted cyclopropyl carbon of a radical-cation intermediate, generated from the bicyclic aryl sulfide **A** by the CAN-oxidation, with an inversion of configuration, the desired β-chlorinated bicyclic acetal **B** could be obtained with high stereoselectivity.[8] Then the targeted cis-fused bicyclic ether **C** would be prepared by the subsequent silane-reduction of **B**. The obscure point of this strategy is the stability of a chloride anion to the conditions of the CAN oxidation.[9] However, we have succeeded in the stereoselective introduction of a chloride to the sterically hindered position of tetrahydropyran rings based on this idea. Herein we describe these results along with the effects of the C4-substituent and arylthio group of **A** on the CAN-mediated ring-opening reaction.

At first, we tried the CAN-oxidation of **1a**, which has no substituent on the C4-position, to examine whether a chloride anion can tolerate the CAN conditions (Scheme 2). After many experiments, the combination of a solvent and a chloride source was revealed to be crucial for this oxidation, and the use of Me_4NCl or H_4NCl in methanol led to the best result. The treatment of **1a** with CAN (5 equiv.) and Me_4NCl (5 equiv.) in dry methanol in the presence of activated molecular sieves 3A gave rise to the chlorinated products **2a** and **3a** as a single isomer in 34% and 33% yields, respectively. If this oxidation was performed in other solvents such as DMF and THF, the corresponding sulfoxide was formed as a single product. Moreover, the employment of *n*-Bu_4NCl as a chloride source prevents the ring-opening reaction of **1a**, resulting in recovery of the starting material. As **3a** could be converted to **2a** in 51% yield by the acidic treatment (*p*-TsOH in benzene at room temperature), both **2a** and **3a** have the same configuration at the chlorinated carbon.



1a-c **2a-c** **3a-b** **4c**

Scheme 2. a: R = H, b: R = α-$(CH_2)_3BOM$, c: R = β-Et

To next investigate the effect of the C4-substituent on this reaction, **1b** and **1c** were subjected to the same conditions described above. Surprisingly, **1b**, bearing an α-substituent at C4, underwent smooth ring-opening to give the desired products **2b** and **3b** in 35% and 48% yields, while **1c**, bearing a β-substituent at C4,

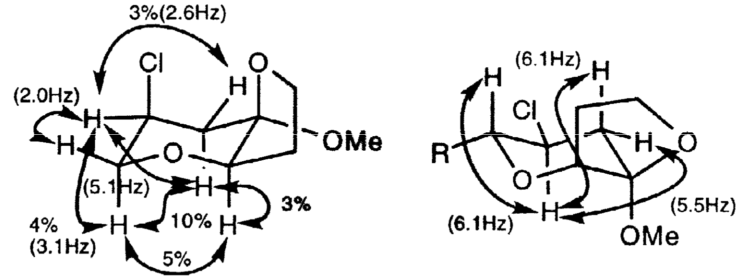
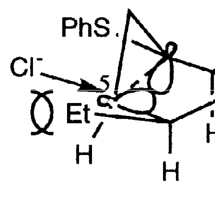


Fig. 1. The NOE (%) and coupling constants (the values in parentheses, Hz) of **2a** and **2b**

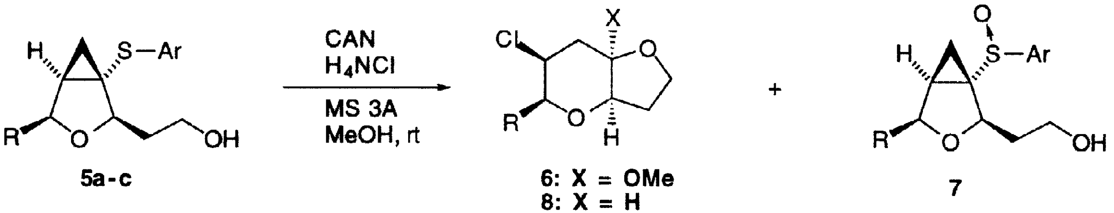


D

Fig. 2. The transition state of the oxidative ring-opening of **1c** by a chloride anion

resisted cleavage of the cyclopropyl bond and gave the corresponding sulfoxide **4c** in 17% yield with the recovered starting material (33%) and a small amount of **2c** (8%). The stereochemistry of **2a** and **2b** was determined from their NOE experiment and coupling constants, which are shown in Fig. 1. These results imply that the introduction of the chloride to **1a**, **b** proceeded highly regio- and stereo-selectively with an inversion of configuration as well as the C-O bond-formation reported previously.[6] The resistance to the ring-opening of **1c** is rationalized by the transition state **D** (Fig.2). Since the cleavage of the cyclopropyl bond by the chloride anion occurs from the upper-left site,[10] the presence of the β-substituent at C4 would prevent the nucleophile approaching to C5.

Table 1. The CAN-Mediated Oxidation of Aryl Sulfides **5a-c** in the Presence of H_4NCl



Substrates 1 and 5		Oxidation	Yield (%)[b]	
Ar	R	Potential (V vs SCE)[a]	**6**	**7**
1c (phenyl)	Et	1.58	8	17
5a (2,6-dimethylphenyl)	Et	1.68	51	24
5b (4-methoxyphenyl)	$(CH_2)_2OBOM$	1.38	0	89
5c (4-chlorophenyl)	$(CH_2)_2OBOM$	1.78	No Reaction	

[a] The oxidation potentials were determined from cyclic voltammetry experiments using a glassy carbon disk electrode in 0.1 M Et_4NOTs/CH_3OH (sweep rate 0.1 V/s). [b] Isolated yield

Finally, expecting to overcome the difficulty of the ring-opening reaction of **1c** and suppress the formation of a sulfoxide, we synthesized several aryl sulfides **5a-c** to examine the effects of steric hindrance and oxidation potential[11] of a sulfur atom on this ring-opening reaction. The represented results of the CAN-oxidation of **5a-c** are listed in Table 1, from which it is seen the 2,6-dimethylphenyl sulfide **5a**, which has a bulkier aryl group on the sulfur atom, is the substrate of choice. Indeed, the CAN-oxidation of **5a** proceeded smoothly at room temperature to afford the desired product **6** in 51% yield as a single isomer along with the sulfoxide **7a** as a minor adduct. Neither **5b**, possessing less positive oxidation-potential, nor **5c**, possessing more positive oxidation-potential, gave the chlorinated product **6**. The similarity of ^{1}H-NMR spectrum of **6** with that of **2a** and NOE studies indicate that **6** has the proper stereochemistry and also adopts the desired conformation. To demonstrate the further utility of this strategy, the obtained product **6** was converted to the β-chlorinated bicyclic ether **8**. The treatment of **6** with triethylsilane and trimethylsilyl triflate in dichloromethane at -30 ℃ gave the desired product **8** stereoselectively without any over-reduction and epimerization (83% yield).[12]

In conclusion, a reliable and stereoselective method for the synthesis of cis-fused bicyclic acetals and ether with a sterically hindered- and axially oriented- chloride atom has been developed. Further study on the application to asymmetric synthesis of dactomelynes is now in progress.

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REFERENCES AND NOTES

1. (a) Gribble, G. W. *Prog. Chem. Org. Nat. Prod.* **1996**, *68*, 1. (b) Naturally-Produced Organohalogens, Grimvall, A.; de Leer, E. W. B. Ed.; Kluwer Academic Publishers. The Netherlands, 1995. (c) Erickson, K. L. In Marine Natural Products, Scheuer, P. J., Ed.; Academic Press, New York, 1983: Vol. V, pp 131-257. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223.
2. Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141-152.
3. Harding, K. E.; Tiner, T. H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I. Ed, Pergamon Press; New York, 1991: Vol. 4, pp 363-421. (b) Miyashita, K.; Tanaka, A.; Shintaku, H.; Iwata, C. *Tetrahedron* **1998**, *54*, 1395-1406. (c) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345-4348. (d) Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett* **1992**, 204-206. (e) Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synthetic Commun.* **1992**, *22*, 1863-1870. (f) Gao, L.; Saitoh, H.; Feng, F.; Murai, A. *Chem. Lett.* **1991**, 1787-1790. (g) Kozikowski, A. P.; Lee, J. *Tetrahedron Lett.* **1988**, *29*, 3053-3056. (h) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173-1174. (i) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560-1563.
4. (a) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863-870. (b) another synthetic study on halotetrahydropyrans: Martin, V. S.; Palazon, J. M. *Tetrahedron Lett.* **1992**, *33*, 2399-2402.
5. Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.*, **1995**, *117*, 8017-8018.
6. (a) Takemoto, Y.; Ohra, T.; Koike, H.; Furuse, S.; Iwata, C.; Ohishi, H. *J. Org. Chem.* **1994**, *59*, 4727-4729. (b) Takemoto, Y.; Ohra, T.; Furuse, S.; Koike, H.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1529-1530.
7. Takemoto, Y.; Furuse, S.; Koike, H.; Ohra, T.; Iwata, C.; Ohishi, H. *Tetrahedron Lett.*, **1995**, *36*, 4085-4088.
8. (a) Wang, Y.; Tanko, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 8201-8208. (b) Dinnocenzo, J. P.; Zuilhof, H.; Liebeerman, D. R.; Simpson, T. R.; McKechney, M. W. *J. Am. Chem. Soc.* **1997**, *119*, 994-1004. (c) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. Soc.* **1997**, *119*, 987-993.
9. Kimura, M.; Kobayashi, K.; Yamamoto, Y.; Sawaki, Y. *Tetrahedron* **1996**, *52*, 4303-4310.
10. (a) Herbertz, T; Roth, H. D. *J. Am. Chem. Soc.* **1997**, *119*, 9574-9575. (b) Shaik, S.; Reddy, A. C.; Ioffe, A.; Dinnocenzo, J. P.; Danovich, D.; Cho, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 3205-3222. (c) Wong, H. N. C.; Hon, M. -Y.; Tse, C. -W.; Yip, Y. -C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198.
11. Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.*, **1996**, *37*, 3157-3160.
12. Alvares, E.; Perez, R.; Rico, M.; Rodoriguez, R.M.; Martin, D. *J. Org.Chem.* **1996**, *61*, 3003-3016.