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Allylic Lithium Oxyanionic Directed and Facilitated Simmons–Smith Cyclopropanation: Stereoselective Synthesis of (±)-*cis*-Sabinene Hydrate and a Novel Ring Expansion

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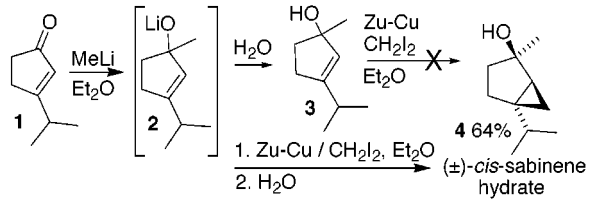
ABSTRACT



The lithium salts of acid-sensitive allyl alcohols, which themselves decompose during Simmons–Smith cyclopropanation, undergo smooth cyclopropanation in the usual stereocontrolled manner. This concept is applied to the most efficient synthesis of (±)-*cis*-sabinene hydrate and to the cyclopropanation of the anion of a nonisolable allyl alcohol resulting upon workup in a ring-expanded enone. The cyclopropanations are also faster for the lithium salts than for the allyl alcohols themselves.

The Simmons−Smith[1] reaction and its variants are probably the most widely used methods of formation of cyclopropanes, compounds of enormous importance as reactive substrates for further transformations.[2] In addition, many are very important in their own right, especially because they are often biologically active.[3] A major advance in this field was afforded by the discovery that allylic and homoallylic hydroxyl groups accelerate and exert great stereochemical control over Simmons−Smith cyclopropanations of alkenes.[4] Recently, a great deal of use has been made of this phenomenon in the induction of enantioselectivity in the reaction.[1b,5]

Some allylic alcohols, however, are acid-sensitive and are destroyed by the Simmons−Smith conditions.[6] There is little doubt that this is the reason for the reported failure in the

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(2) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

(3) Salaün, J. In *Small Ring Compounds in Organic Synthesis (VI)*; Meijere, A., Ed.; Springer: Berlin, 2000; pp 1−64.

(4) (a) Winstein, S.; Sonnenberg, J.; DeVries, L. *J. Am. Chem. Soc.* **1959**, *81*, 6523−6524. Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, 91, 6892−6894 and references therein. (b) Dauben, W. G.; Berezin, G. H. *J. Am. Chem. Soc.* **1963**, *85*, 468−472. (c) For an excellent review including directed Simmons−Smith cyclopropanations, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(5) Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197−1207. Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943−11952 and citations therein. Denmark, S. E.; Christenson, B. L.; O'Conner, S. P.; Murase, N. *Pure Appl. Chem.* **1996**, *68*, 23−27.

(6) Some examples: Kelly, D. P.; Leslie, D. R.; Smith, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 687−694. Nash, G.; Waring, A. J. *J. Chem. Res., Miniprint* **1988**, 1811−1823. Bessmertnykh, A. G.; Bubnov, Y. N.; Voevodskaya, T. I.; Donskaya, N. A.; Zykov, A. Y. *Zh. Org. Khim.* **1991**, *26*, 2348−2355. Tori, M.; Hamaguchi, T.; Aoki, M.; Sono, M.; Asakawa, Y. *Can. J. Chem.* **1997**, *75*, 634−640.

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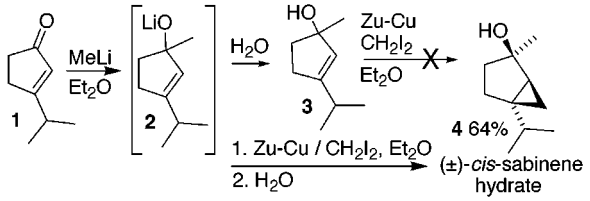
attempt to cyclopropanate the allyl alcohol **3** to (±)-*cis*-sabinene hydrate **4** (Scheme 1).[7] The tertiary alcohol **3** was

Scheme 1

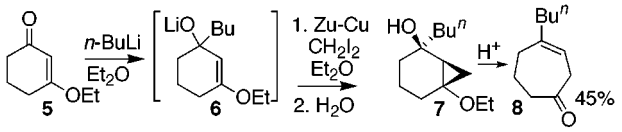


reported to be "extremely unstable" and "when subjected to a Simmons−Smith reaction, decomposed rapidly and no bicyclic product could be isolated."[7] The allylic carbocation derived by acid-induced dehydroxylation of **3** would be exceptionally stable in view of the tertiary nature of both of its termini. Since we required a sample of **4** for comparison with one that we had synthesized as a demonstration of the use of a new synthetic procedure based on the lithium-ene cyclization,[8] we sought to surmount this obstacle.

We now present an operationally extremely simple and apparently general solution to the instability of certain alcohols under Simmons−Smith cyclopropanation conditions. The procedure is illustrated with the most efficient synthesis of (±)-*cis*-sabinene hydrate **4** (Scheme 1). The ketone **1**[7] is treated with methyllithium in dry ether at −78 °C. After the reaction mixture is warmed to 0 °C, the resulting lithium alkoxide **2** is subjected directly to the Simmons−Smith conditions[9] to provide the racemic natural product in 64% yield.[10] Thus, not only is the reaction successful in the presence of the allylic oxyanionic group, but even had the conversion of **3** to **4** been successful, the route from **1** is shorter than that which would proceed through **3**.

The lithium oxyanion mediated procedure also allows one to cyclopropanate allylic alcohols that cannot be isolated. This is demonstrated by the alkylative ring expansion shown in Scheme 2. The butyllithium adduct **6**, the corresponding alcohol of which is expected to be too unstable to isolate (rearranging to a 3-substituted cyclohexen-2-one upon treat-

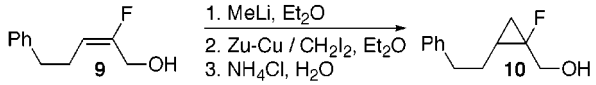
Scheme 2



ment with ice[11]) was subjected to the Simmons−Smith reaction. The product **7**[12] was immediately subjected to a catalytic amount of HCl, leading to the ring expansion[13] product **8**. Thus, in this case the conventional allylic hydroxy-directed cyclopropanation is unavailable and the lithium oxyanionic version is a considerable advance.

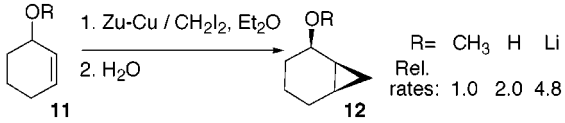
Since it is well established, as indicated above, that allylic hydroxyl groups facilitate Simmons−Smith cyclopropanations via complexation of the organozinc intermediate with the hydroxyl group, it seemed possible that the lithium oxyanionic group could be even more activating. Two tests of this concept were applied. In the first, we attempted to cyclopropanate the conjugate base of **9**, which had been reported[14] to be unreactive toward 1.1 equiv of Simmons−Smith reagent. Indeed, the inseparable mixture of product and unreacted starting material contained 44% of the cyclopropane (NMR, Scheme 3). In the second test, a large

Scheme 3



excess of an equimolar amount of the of the allyl methyl ether **11** (R = CH_3)[15] and the corresponding allylic lithium

Scheme 4



oxyanion **11** (R = Li) was subjected to the standard cyclopropanation conditions.[9] The cyclopropanation products

(7) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1968**, *33*, 1656−1659.
(8) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−413.
(9) In the experiments described in this paper, the zinc−copper couple is prepared freshly according to Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825−1826. The following general cyclopropanation procedure is based on that of Dauben.[4b] MeLi (0.80 mL, 1.40 M in ether, 1.12 mmol) was added under argon to a solution of enone **1** (1.0 mmol) dissolved in ether (5 mL) at −78 °C, and the reaction mixture was warmed to 0 °C before it was cannulated into a suspension of Zn−Cu couple(180 mg, 2.75 mmol), I_2 (1 mg), and CH_2I_2 (576 mg, 2.15 mmol) in ether (20 mL). The reaction mixture was heated at reflux for 2 h. It was then diluted with ether (3 × 25 mL), and the organic phase was decanted. The latter was washed with 5% K_2CO_3 (2 × 30 mL), brine (50 mL), and water (50 mL) and dried (K_2CO_3). The solvent was removed to give an oily residue that was subjected to column chromatography to give 99 mg (0.64 mmol, 64% yield) of the cyclopropanation product **4**.
(10) For previous syntheses of (±)-*cis*-sabinene hydrate **4**, see refs 7 and 8 and Gaoni, Y. *Tetrahedron* **1972**, *28*, 5525−5531.
(11) Woods, G. F.; Griswold, P. H., Jr.; Armbrecht, B. H.; Blumenthal, D. I.; Plapinger, R. *J. Am. Chem. Soc.* **1950**, *72*, 1645−1648.
(12) Bicyclic **7** can be isolated by careful column chromatography with 1% NEt_3 in the eluent (hexanes/ethyl acetate 4:1). A reasonable ^1H NMR spectrum was obtained, but it was not further characterized because of its instability. The 45% yield of **8** was obtained by treating the crude **7** with a catalytic amount of HCl.
(13) Wenkert, E.; Buckwalter, B. L.; Sathe, S. S. *Synth. Commun.* **1973**, *3*, 261−264.
(14) Morikawa, T.; Sasaki, H.; Mori, K.; Shiro, M.; Taguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 3189−3193.
(15) Shono, T.; Ikeda, A. *J. Am. Chem. Soc.* **1972**, *94*, 7892−7898. Damico, R. *J. Org. Chem.* **1968**, *33*, 1550−1556.

12 (R = CH_3)[16] and **12** (R = H)[17] were separated, and the relative quantities were analyzed by gas-phase chromatography−mass spectrometry.[18] The ratio of **12** (R = H) to **12** (R = CH_3) was found to be 4.75 ± 0.15. Chan and Rickborn[19] had previously reported that the ratio of rates of cyclopropanation of **11** (R = H) to **11** (R = CH_3) is 2 ± 0.2 Thus, converting the allylic alcohol group into its conjugate base increases the rate of cyclopropanation by a factor of 2.4. Both experiments show that the use of an allylic oxyanionic group facilitates the Simmons−Smith procedure much as such a group facilitates metallo-ene cyclizations as recently reported from this laboratory.[8,20]

In summary, the use of the lithium salts of allylic alcohols rather than the alcohols themselves can have two major advantages in classical allylic hydroxyl-directed Simmons−Smith cyclopropanations.[21] Nonisolable allyl alcohols or acid-sensitive allyl alcohols that are unstable to the Simmons−Smith conditions are readily cyclopropanated, and if the alcohol is produced by addition of an organolithium to a carbonyl group, it is not necessary to isolate the alcohol itself. Finally, cyclopropanation of the lithium salt is more facile than that of the corresponding alcohol. It is probably prudent to use the lithium salt rather than the alcohol in the first attempt provided that it can be generated without destruction of other functional groups.

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(16) Daino, Y.; Hagiwara, S.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1989**, 275−282.

(17) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525−3532. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

(18) It was determined using a mixture of the two products of known compostion that the ratio of the two products as determined by integration of the peaks in GC−MS was identical to that determined by integration of appropriate peaks in the ^{1}H NMR spectrum of the same mixture.

(19) Chan, J. H.-H.; Rickborn, B. *J. Am. Chem. Soc.* **1968**, *90*, 6406−6411.

(20) Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.*, **2001**, *123*, 30−34.

(21) The lithium salt of a cyclopent-2-ene-1-ol was reported by Corey and Virgil to be cyclopropanated under Simmons−Smith conditions, and their procedure was then used by Saxton et al. in a very similar system. However, there was no indication as to why the lithium salt was used. Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429−6431. Guile, S. D.; Saxton, J. E.; Thornton-Pett, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1763−1767.