Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also thank the UCSB Committee on Research for partial support.

References and Notes

(1) (a) E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975); (b) R. N. Gedye, P. Arora, and A. H. Khalil, *Can. J. Chem.*, **53**, 1943 (1975); (c) H. A. Dieck and R. F. Heck, *J. Organomet. Chem.*, **93**, 259 (1975); (d) I. Kuwajima and Y. Doi, *Tetrahedron Lett.*, 1163 (1973); (e) E. W. Della and M. Kendall, *Aust. J. Chem.*, **22**, 2351 (1969); (f) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **29**, 821 (1974); (f) W. Herz, *J. Am. Chem. Soc.*, **78**, 1485 (1956); (g) A. Chatterjee, *Tetrahedron Lett.*, 959 (1965); (h) F. Korte and O. Behner, *Chem. Ber.*, **89**, 2675 (1956); (i) M. Julia and D. Arnould, *Bull. Soc. Chim. Fr.*, No. 2, 743 (1955).

(2) There are a few scattered reports of cyclopropane formation from the reaction of methyl 4-bromocrotonate with nucleophiles. Specifically, Rambaud[2a] has reported that the addition of sodium methoxide (and ethoxide) to the crotonate leads to a low yield of methyl-2-methoxycyclopropane. This result was also reported by Owen and Sultanbawa.[2b] However, Dreiding and Pratt[2c] later showed that the material previously presumed to be the cyclopropane was instead dimethyl 2,4,6-octatrienedioate. It appears that the only bona fide example is due to English[2d] wherein inverse addition of phenylmagnesium bromide to methyl 4-bromocrotonate afforded a 13% yield of the cyclopropane product. (a) R. Rambaud, *C. R. Hebd. Seances Acad. Sci.*, **200**, 2089 (1935); R. Rambaud, *Bull. Soc. Chim. Fr.*, **5**, 1595 (1949). (b) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3098 (1949). (c) A. Dreiding and R. Pratt, *J. Am. Chem. Soc.*, **75**, 4580 (1953). (d) R. Ratney and J. English, Jr., *J. Org. Chem.*, **25**, 2213 (1960).

(3) We routinely use mercaptides to effect displacement of bromide from methyl 2-bromomethylacrylate for the synthesis of the corresponding acyclic sulfides.

(4) New compounds were characterized using IR, ^{1}H NMR, mass spectral analysis, combustion analysis, and occasionally ^{13}C NMR.

(5) The idea of forming cyclopropanes via Michael addition followed by elimination is not new. However, in each of the routes which has been used previously, the leaving group is attached to the incoming attacking carbon atom. Thus the leaving group (heteroatom) is lost rendering heteroatom substituted cyclopropanes much less readily accessible. In our route, the heteroatom (sulfur) is the attacking group and remains attached to the resulting cyclopropane. See H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, pp 614, 689, 719–721, and references cited therein.

(6) For example, see (a) Y.-Ho. Chang and H. W. Pinnick, *J. Org. Chem.*, **43**, 373 (1978); (b) C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, **95**, 7692 (1973); (c) W. E. Truce and L. B. Lindy, *J. Org. Chem.*, **26**, 1463 (1961); (d) E. Wenkert, D. A. Berges, and N. F. Golob, *J. Am. Chem. Soc.*, **100**, 1263 (1978); (e) E. Wenkert, B. L. Buckwalter, A. C. Craveiro, E. L. Sanchez, and S. S. Sathe, *ibid.*, **100**, 1267 (1978); (f) E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3684 (1975); (g) B. M. Trost, D. E. Keeley, H. C. Arndt, J. H. Rigby, and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **99**, 3080 (1977); (h) B. M. Trost, D. E. Keeley, H. C. Arndt, and M. J. Bogdanowicz, *ibid.*, **99**, 3088 (1977), and references therein.

(7) (a) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 725 (1967); (b) J. F. Bunnett and D. Greary, *J. Org. Chem.*, **39**, 3173, 3611 (1974); (c) M. M. Baizer, J. L. Chruma, and P. A. Berger, *ibid.*, **35**, 3569 (1970); (d) J. A. Zaltewiez and T. M. Oestreich, *J. Am. Chem. Soc.*, **95**, 6863 (1973).

(8) It is, of course, still possible that an electron-transfer process may still be occurring. Our results simply require that the radicals collapse before diffusion from the solvent cage and subsequent trapping.

R. Daniel Little,* James R. Dawson

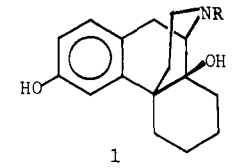
Department of Chemistry, University of California
Santa Barbara, California 93106

Received April 10, 1978

A Stereoselective Total Synthesis of 14-Hydroxymorphinans. Grewe Approach

Sir:

The 3,14-dihydroxymorphinans have been synthesized by modification of thebaine[1] and by total synthesis.[2] Since a number of these compounds have shown interesting biological properties, in particular, clinically effective analgesia[2,3] (butorphanol, **1a**) and strong narcotic antagonism[2] (oxilorphan, **1b**), a new synthesis in which optical resolution could be accomplished at an earlier step was desirable. Thus a modification of the classical Grewe synthesis of morphinans[4,5] to the synthesis of 14-hydroxymorphinans, using a common intermediate 1-*p*-methoxybenzyloctahydroisoquinoline (**2a**) (Scheme I) attracted our attention.[6]



1

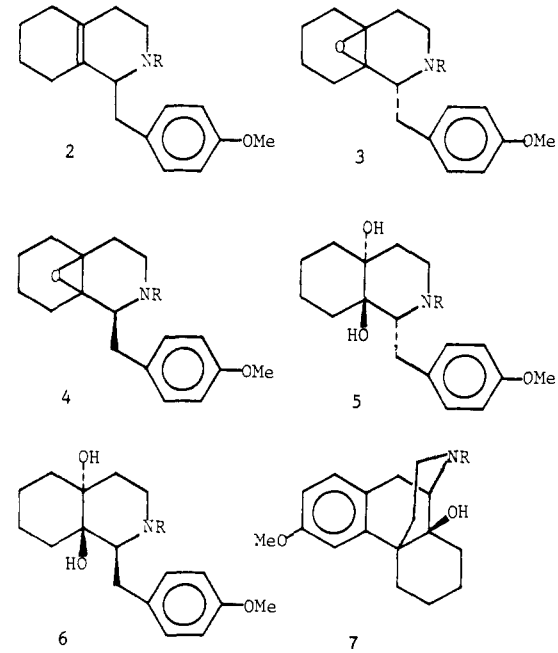
a) butorphanol R = CH_2-◇

b) oxilorphan R = CH_2-◁

We now report on the first successful synthesis of 14-hydroxymorphinans via a Grewe synthesis, using **2a** as starting material. An initial attempt was to epoxidize amide **2b** (mp 75–78 °C),[7] to the corresponding trans epoxide (**3b**), which would be expected to undergo a direct one-step acid-catalyzed epoxide opening–cyclization, to give **7b.** However, a mixture of epoxides was obtained in which **4b** was the major product, and thus an efficient direct cyclization was precluded. The mixture was separated by column chromatography to give **4b** (mp 84–86 °C from petroleum ether) and **3b** (mp 102–105 °C) in 9:1 ratio. Treatment of **4b** with sodium borohydride in ethanol under reflux for 1 h gave **4a,** an oil, in quantitative yield, whereas **3b** required treatment for 20 h under the same reaction conditions to give **3a** (mp 69–70 °C). Acid-catalyzed hydrolysis of **4a** gave stereoselectively the product of C-10 opening, the diol **6a** (mp 159–160 °C), while the same treatment of **3a** resulted in a 7:3 mixture of **5a** (mp 156–157 °C) and **6a,** respectively. In contrast to these results, acid-catalyzed opening of epoxide **3b** gave exclusively the product of C-10 opening, the trans diol **5b** (mp 103–105 °C), whereas **4b** gave a mixture of 46% **5b** and 54% **6b** (mp 84–85 °C).

The structure and stereochemistry of the diols was indicated by the fact that both **5a** and **5b** upon treatment with phosphoric acid (5 days, 65 °C) gave 14-hydroxymorphinan (**7a**), albeit in yields (4–6%) and with decomposition of starting materials. However, under the same reaction conditions, **6a** and **6b** were completely destroyed. The structural assignments of **5a** and **6a** were confirmed by an x-ray crystallographic study,[8] which

Scheme I



a) R = H, b) R = $COCF_3$, c) R = CO-◇,

d) R = CH_2-◇, e) R = CH_3

0002-7863/78/1500-4609$01.00/0

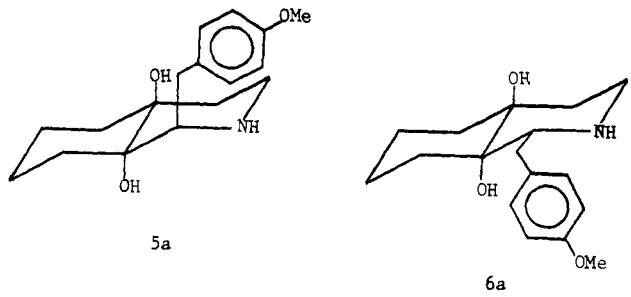


Figure 1.

showed that these compounds exist in the conformations shown in Figure 1. The stereochemistry of epoxides was deduced from the expected exclusive or preferential C-10 opening by analogy to previous results in the *N*-methyl series (**3e, 4e**) by Onda et al.[6] and in the *N*-methyloctahydroisoquinoline series by Grob and Wohl.[9]

Clearly, for the practical synthesis of 14-hydroxymorphinans a stereoselective C-9 opening of a suitable cis epoxide **4** to a diol **5** and an efficient cyclization of **5** to **7** were essential. The first indication that the cyclization step may be improved was obtained in the reaction of borane complex of **5a** with phosphoric acid. This reaction was cleaner (no destruction of starting material was observed), the reaction time was shorter (4–5 h), and the yield of **7a** was higher (14–16%). Finally, yields in both the epoxide opening and the diol cyclization were further dramatically improved with the introduction of various other substituents on the nitrogen atom as illustrated below for the synthesis of butorphanol.

Acylation of **2a** by a standard procedure readily afforded the amide **2c** (mp 89–91 °C). Epoxidation of **2c** with *m*-chloroperbenzoic acid gave a 1:4 mixture of **3c** (mp 118–120 °C) and **4c** (mp 77–78 °C), which was separable by column chromatography. Acid-catalyzed opening of **3c** gave stereoselectively the product of C-10 opening, the trans diol **5c** (mp 148–150 °C). The same diol was the major product of the reaction of the cis epoxide **4c** indicating a stereoselective opening at C-9. The ratio of **5c** to **6c** (mp 90–92 °C) was 7:3. When the mixture of epoxides (**3c** and **4c**) in 2-butanone was treated with 64% sulfuric acid for 16 h, followed by addition of water, removal of organic solvent by distillation, and heating of the aqueous phase under reflux for 1 h, the trans diol **5c** crystallized upon cooling in 75% overall yield from **2a.** Reduction of **5c** with $LiAlH_4$ gave **5d** (92%, mp 120–122 °C). Treatment of a solution of **5d** in THF with slight excess of BH_3–THF, followed by concentration and treatment of the residual solid borane complex with 15 parts of anhydrous phosphoric acid at 40–45 °C for 16 h gave, after workup, **7d,** in 65–70% yield. Demethylation of **7d** to **1a** has been described earlier.[2]

This synthesis was successfully repeated with optically active **2a,**[10] giving the optically active **7d,** thus eliminating costly last-step resolution in the original synthesis.[2]

The use of amine–borane complex in Friedel–Crafts-type cyclization, to the best of our knowledge, has not been previously recorded, although its use as a protective group in intermolecular oxidative phenol coupling[11] and transformation of proerythrinodienone to aporphine[12] has been described recently.

References and Notes

(1) Y. K. Sawa and H. Tada, *Tetrahedron*, **24**, 6185 (1968).
(2) (a) I. Monković, H. Wong, A. W. Pircio, Y. G. Perron, I. J. Pachter, and B. Belleau, *Can. J. Chem.*, **53**, 3094 (1975); (b) I. Monković, T. T. Conway, H. Wong, Y. G. Perron, I. J. Pachter, and B. Belleau, *J. Am. Chem. Soc.*, **95**, 7910 (1973).
(3) M. Tavakoli, G. Corrsen, and F. S. Caruso, *Anesth. Anal. (Cleveland)*, **55**, 394 (1976), and references therein.
(4) R. Grewe, *Naturwissenschafen*, **33**, 33 (1946).
(5) (a) O. Shnider and J. Hellerbach, *Helv. Chim. Acta*, **32**, 821 (1949); (b) *Ibid.*, **34**, 2218 (1951).
(6) This type of the synthesis of 14-hydroxymorphinans has been attempted by M. Onda, Y. Sugama, H. Yokoyama, and F. Tada, *Chem. Pharm. Bull.*, **21**, 2359 (1973).
(7) All compounds described herein gave analytical and spectral data in agreement with the postulated structures.
(8) F. R. Ahmed, *Acta Crystallogr., Sect. B*, in press.
(9) C. A. Grob and R. A. Wohl, *Helv. Chim. Acta*, **49**, 2175 (1966).
(10) H. C. W. Den, W. Leimgruber, and E. Mohacsi, German Patent 2 003 486; *Chem. Abstr.*, **73**, 77081a (1970).
(11) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 613 (1973).
(12) S. M. Kupchan and C. K. Kim, *J. Org. Chem.*, **41**, 3112 (1976).

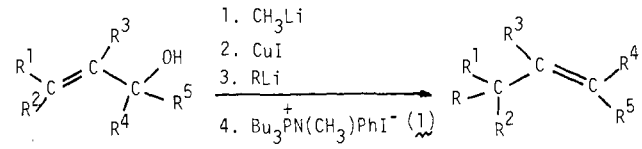
Ivo Monković,* Carol Bachand, Henry Wong
Bristol Laboratories of Canada
Candiac, Quebec, Canada J5R 1J1
Received February 23, 1978

Regio- and Stereoselective γ Substitution of Allylic Alcohols with Alkyllithium Compounds by Using *N,N*-Methylphenylaminotributylphosphonium Iodide. Anti Stereochemistry of S_N2' Reaction[1]

Sir:

The carbon–carbon bond formation by direct substitution of a hydroxyl group of allylic alcohols with a carbon moiety is one of the most attractive pathways for synthesis of olefinic compounds, since allylic alcohols are often naturally occurring key intermediates[2] and many highly selective, potentially useful methods for synthesis of allylic alcohols have recently been explored.[3]

Previously, we reported that the regioselective synthesis of olefins by coupling of allylic alcohols with organolithium compounds using *N,N*-methylphenylaminotriphenylphosphonium iodide.[4] We now wish to report that the selective γ-alkylation of allylic alcohols with organolithium compounds in conjunction with *N,N*-methylphenylaminotributylphosphonium iodide (**1**) proceeds as depicted in eq 1. The alkylation provides an efficient single-step process for regio- and stereoselective synthesis of olefins from allylic alcohols. It is expected that the process will find widespread use and that in many instances it will be found superior to current procedures.[5-7]



(1)

Reagent **1** is easily prepared by the addition of the equivalent of phenyl azide to tributylphosphine in ether at reflux, followed by treatment with excess methyl iodide at reflux in 90% yield, mp 120–120.5 °C (recrystallized from ethyl acetate). The following procedure for the preparation of *trans*-5-undecene is representative of the alkylation. To a suspension of cuprous iodide (1.90 g, 10 mmol) in dry THF (20 mL) was added a solution of the lithium allyloxide, prepared in a separate flask from 1-hepten-3-ol (1.14 g, 10 mmol) and ethereal methyllithium (1.23 M, 8.2 mL) at 0 °C, with stirring at room temperature. After additional stirring for 30 min, the resulting green-brown solution was cooled to −78 °C, and then a solution of butyllithium in hexane (1.34 M, 7.4 ml) was added over a 5-min period. Subsequently, to the resulting brown suspension a solution of **1** (4.35 g, 10 mmol) in dry DMF (40 mL) was added at the same temperature, and the reaction mixture was allowed to warm to room temperature. The brown suspension became a homogeneous solution. After additional stirring for 3 h, ether and an aqueous saturated NH_4Cl solution were added to the reaction mixture (at 0 °C), which was then fil-

0002-7863/78/1500-4610$01.00/0