

the mobility of the ions in the ionic solution is accelerated by increasing pressure so that the average distance between the opposite ions decreases. This fact explains the decrease of the ionic charge, which results the decrease in the ionic activity. Second, the degree of hydrogen bonding of water molecules can be increased with pressure, which decreases the ionic charge to give a decrease in ionic activity.¹⁵

From the equations of (1), (2), and (5), we derived the next equations.¹⁶

$$\begin{aligned} \Delta V_{Na^+} &= \Delta V_{Na^+}(L) - \Delta V_{Na^+}(H) \\ &= -RT(\partial \ln \gamma_{Na^+}(L)/\partial P)_{T,m} + RT(\partial \ln \gamma_{Na^+}(H)/\partial P)_{T,m} \end{aligned} \quad (10)$$

Assuming that the activity coefficients of ions in the dilute concentration is not dependent on pressure, we can obtain the Eqn (11) from the Eqn (10).

$$\Delta V_{Na^+} = -RT(\partial \ln \gamma_{Na^+}(H)/\partial P)_{T,m} \quad (11)$$

Similarly we can get the next equations.

$$\Delta V_{Cl^-} = -RT(\partial \ln \gamma_{Cl^-}(H)/\partial P)_{T,m} \quad (12)$$

$$\Delta V_{Br^-} = -RT(\partial \ln \gamma_{Br^-}(H)/\partial P)_{T,m} \quad (13)$$

The volume changes of the sodium, chloride, and bromide ions which had been calculated from these equations were listed in Table 7. The ΔV_{ion} values are negative and decrease with pressure. This fact is attributed to the electrostriction between the ion and water molecules. It can be also illustrated that the hydration of the ions increases with pressure to diminish the ionic charge of the ions and so the activity of the ions decreases.

Acknowledgement. The Present Studies were Supported by the Basic Science Research Institute Program, Ministry of Education, 1984.

References

1. I. Kagawa and K. Katsura, *J. Polymer Sci.*, **17**, 365 (1955).
2. M. Nagasawa and I. Kagawa, *ibid.*, **25**, 61 (1957).
3. A. Katchalsky and S. Lifson, *ibid.*, **11**, 409 (1953).
4. F. Osawa, N. Imai, and I. Kagawa, *ibid.*, **13**, 93 (1954).
5. D.I. Hitchcock, *J. Am. Chem. Soc.* **50**, 2076 (1928).
6. A.S. Brown and D.A. MacInnes, *ibid.*, **57**, 1356 (1935).
7. T. Shedlovsky, *ibid.*, **72**, 3681 (1950).
8. T. Shedlovsky and D.A. MacInnes, *ibid.*, **59**, 503 (1937).
9. J.G. Kirkwood and J.C. Poirier, *J. Phys. Chem.*, **58**, 591 (1954).
10. G.E. Kimball, M. Cutler, and H. Samelson, *ibid.*, **56**, 57 (1952).
11. A. Katchalsky, O. Künzle, and W. Kuhn, *J. Polymer Sci.*, **5**, 283 (1950).
12. H.S. Frank and P.T. Thompson, *J. Chem. Phys.*, **31**, 1068 (1959).
13. R.M. Fuoss and L. Onsager, *Proc. Natl. Acad. Sci. U.S.A.*, **47**, 818 (1961).
14. J.-G. Jee, J.J. Chung and J.U. Hwang, *J. Korean Chem. Soc.*, **18**, 320 (1974).
15. J. E. Desnoyers and B.E. Conway, *J. Chem. Phys.*, **68**, 2305 (1964).
16. G. Hills, "Electrochemistry at High Pressure", 2nd International Congress of Electrochemistry, Melbourne, 1968.

Synthesis of a Conformationally-rigid Etorphine Analogous

Keun Jae Kim*

Department of Chemistry, Han Nam University, Daejeon 300

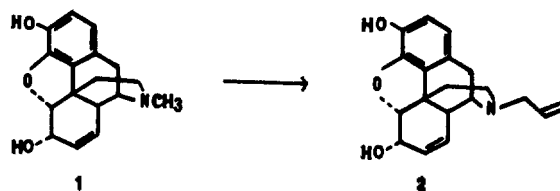
Soon Jong Hahn and Hark Soo Lyu

Department of Chemistry, Yonsei University Seoul 120. Received September 17, 1985

In order to synthesize conformationally rigid etorphine analogues having potentially interesting pharmacological activities, synthesis of compound **3** by the reaction of compound **4** and compound **5** via intramolecular Diels-Alder reaction has been attempted. However, the reaction did not go well and the compound **3** would not be isolated. Therefore, intermolecular Diels-Alder reaction using dimethyl acetylene dicarboxylate was attempted. As shown in scheme 2, Diels-Alder adduct **9** was converted into the target molecule **14** containing the new [2,2,2] bicyclo octane ring in good yields.

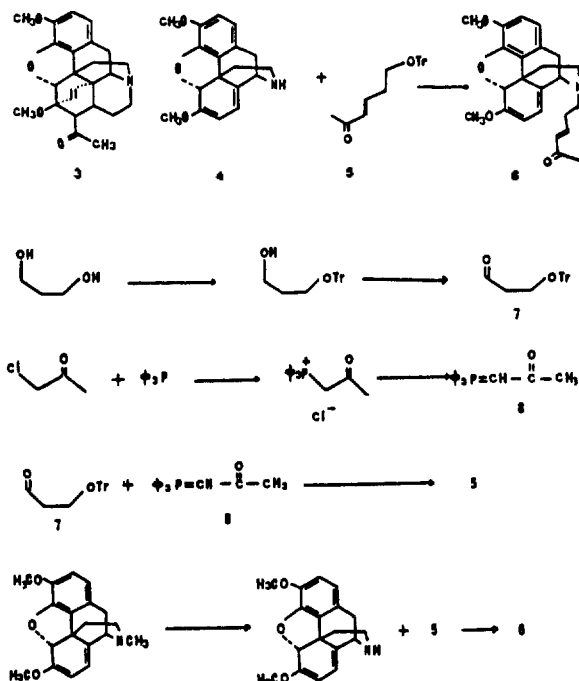
Introduction

Many morphine derivatives possess analgesic activities. Most of these compounds are converted into the compounds with good antagonist activity by the simple substitution of N-methyl group. For example, the agonist morphine **1** is converted into the antagonist nalorphine **2** by changing the methyl group.



Over the years, there have been many theories to explain the difference in biological activities with simple chemical differences. In 1974 Belleau and his coworkers advanced that the spatial orientation of the lone pair of electron on nitrogen is primarily important in determining the biological activity.¹ The same model has been proposed by other workers.² Presumably, the N-methyl group, due to its small size, would occupy the axial position of piperidine ring for a large percent of the time. The methyl group would interact with the opiate receptor and cause morphine-agonist activity. Substitution of the methyl group with the larger allyl group would cause the allyl group to prefer the equatorial conformation and thus interact with the antagonist site of the opiate receptor. The purpose of this project is to prepare the morphine derivatives with the nitrogen substituent held in a defined conformation, either axial or equatorial.

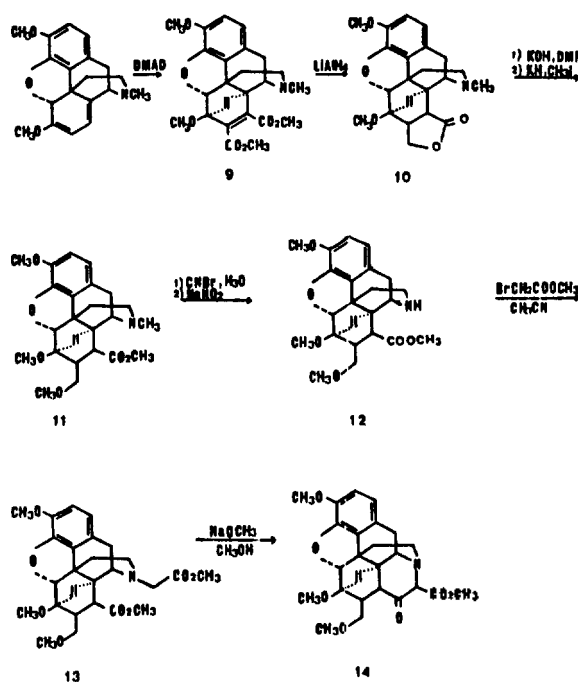
On the basis of previous studies,^{1,3} the target molecule we have chosen is compound 3 in which the nitrogen substitution is tied back to one of the carbon of the [2,2,2] bicyclo octane ring system 3. This would then force the nitrogen substituent into the axial conformation, and according to the theoretical model, this should cause interaction with agonist receptor site. Our synthetic plan was to prepare compound 3 by reacting northebaine 4, prepared from thebaine, with α,β -unsaturated ketone 5 via intramolecular Diels-Alder reaction, although there are few reports in the literature on Diels-Alder reactions with thebaine.^{3,4}



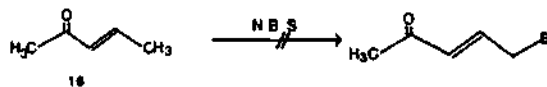
Scheme 1.

Results and Discussions

For the preparation of enone 5, allylic bromination of enone 16 with N-bromosuccinimide was first attempted but a mixture of several products was obtained. Moreover, reaction of northebaine with a mixture of several products obtained from allylic bromination did not give the desired product.



Scheme 2.



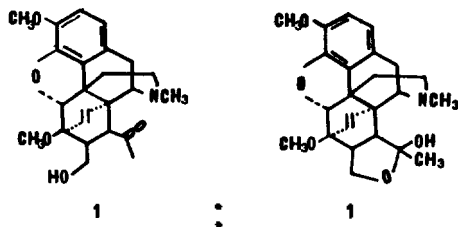
Therefore, we tried another synthetic plan as shown in scheme 1. The northebaine was also synthesized according to literature procedure.⁵ Since 3-trityloxypropanol was a known compound,⁶ 1,3-propanediol was converted to 3-trityloxypropanol by the procedure of Bauman et al.⁷ with a yield of 40%.

The aldehyde was prepared by oxidation with buffered pyridinium chlorochromate.⁸ In order for the Wittig reaction to proceed, another phosphorous ylide was synthesized. Chloroacetone was treated with triphenyl phosphine to form the phosphonium salt which was converted to the phosphorane 8 with aqueous sodium hydroxide. The phosphorane was treated with the aldehyde 7 in benzene to give α,β -unsaturated ketone 5. Removal of trityl ether group was attempted by using benzenesulfonic acid, at 0°C and room temperature. Only decomposition was seen by either TLC or NMR. Attempted cleavage using trimethyl silyl iodide, either the reagent itself⁹ or prepared in situ from trimethylsilylchloride and sodium iodide,¹⁰ also gave no isolable products. Therefore, an attempt was made to first do the Diels-Alder reaction, then convert the trityloxy group into the leaving group. Reaction of α,β -unsaturated ketone 5 with anthracene or thebaine in benzene at reflux temperature gave no adduct by either TLC or NMR. Therefore, we tried the Diels-Alder reactions between thebaine and α,β -unsaturated ketone 5 at high pressure (15 Kbar) for 48h at room temperature and gave many spots by TLC. Further Diels-Alder reaction was not attempted.

When the reaction between thebaine and diethyl acetylene dicarboxylate was carried out, ester 9 was produced. When the ester was reduced with lithium aluminium hydride, a lactone 10 was formed. Similar lactone has been prepared by Bentley¹¹ using the addition of methyl Grignard to the dimethyl maleate/thebaine adduct. Although we attempted to methylate

the lactone by forming the anion with lithium diisopropyl amide (-78°C) and quenching with excess methyl lithium, NMR showed that no methylated lactone had been formed.

There has been one attempt: addition of methyl lithium to the lactone. This gave the hydroxy lactone and the cyclic hemiketal. The NMR spectrum indeed shows the desired compounds, in approximately 1:1 ratio.



The other reaction of lactone **10** which has been investigated is *N*-demethylation. When the lactone was treated with lithium methanthiolate in HMPA, there was no reaction.

A procedure to open the lactone would be the treatment with trimethylxoniumtetrafluoroborate to form the oxonium salt, then treatment with methanol. This procedure gave only recovered starting material. Treatment of lactone **10** with solid potassium hydroxide in dimethyl formamide followed by potassium hydride and then methyl iodide gave a good yield of chromatographed ester-ether, **11**. But we changed the solvent to dioxane and the experiment became reproducible, affording the ester-ether **11** in 70% yield.

When the lactone was treated with cyanogen bromide and hydrolysis in sodium nitrite, it gave nor-ester-ether **12**. The compound **12** was treated with ethyl brooacetate, followed by treatet with sodiu hydroxide gave compound **13** in 60% yield. The compound **13** was treated with sodium methoxide in methanol to give compound **14** in 75% yield. chemical odificatio of compound **14** and biological studies of conformationally rigid etorphine analogues will be the subject of our next research.

Experimental

Infrared spectra were recorded with Shimadzu IR-440 spectrophotometer. Proton NMR were taken on a Bruker WP 80MHz spectrometer, using tetramethyl silane as an internal reference. All solvents and liquids were distilled before use.

3-Trityloxypropanol. A solution of 13.6g (0.18mol) of 1,3-propanediol and 16.8g (0.06mol) of chlorotriphenylmethane in 10 mL of pyridine was stirred at 100°C for 19h. The solution was allowed to cool to room temperature. Water was added and the mixture was extracted with 3×50 mL of ether. The ethereal extracts were washed with water, 0.25M aqueous sulfuric acid, 1% aqueous potassium carbonate, and water. The organic layer was dried over potassium carbonate. Evaporation at reduced pressure gave a solid residue. Heptane (400 mL) was added and the mixture was heated at reflux for 10 min, then allowed to cool to room temperature. The crystalline precipitate was filtered off, washed with cold heptane and air dried and afforded 9.4g (40%) of the alcohol as colorless needles: mp $119-120.5^{\circ}\text{C}$ (lit.¹⁴ $118-120^{\circ}\text{C}$).

3-Trityloxypropanal. A solution of 12.55g (58 mmol) of pyridinium chlorochromate and 0.79g (9.6 mmol) of sodium acetate in 10 mL of dichloromethane was stirred vigorously at room temperature. 7.74g (23 mmol) of alcohol in 45 mL

of dichloro methane was then added in one portion. After 2h, ether was added and the solvent filtered through a small pad of Florosil. The black gummy residue and the product were allowed to solidify to give 6.5g (87%) of aldehyde: mp $100-102^{\circ}\text{C}$ (lit.¹⁵ mp 101°C): $^1\text{H-NMR}$ (CDCl_3) δ : 2.51 (d, $J=6\text{Hz}$, 2H, CH_2 CHO) 7.05-7.4 (m, 15H, ArH) 9.6 (t, $J=2\text{Hz}$, 1H, CHO).

6-Trityloxy-3-hexene-2-one. A solution of 3.6g (11 mmol) of aldehyde ($\text{R}=\text{CPh}_3$) and 3.5g (10.7 mmol) of triphenyl phosphineacetylmethylene in 100 mL of benzene was heated at reflux temperature for 18h. The mixture was allowed to cool to room temperature and the solvent was evaporated. The residue, chromatographed on silica gel using 5% ether-hexane as the eluent, afforded 2.98g (78%) of the unsaturated ketone: $^1\text{H-NMR}$ (CDCl_3) 2.14(s, 3H, CH_3) 2.40(apparent t, $J=6\text{Hz}$, 2H, CH_2) 3.11(t, $J=6\text{Hz}$, 2H, CH_2O), 7.05-7.4(M, 15H, ArH); IR(neat), 2940, 1675, 1635, 1605, 1485, 1445, 1075, 705 cm^{-1} .

6-trityloxy-3-hexene-2-ol. A solution of 2.56g (7.2 mmol) of 6-trityloxy-3-hexene-2-one in 10 mL of ether was added dropwise over 5 min to a mixture of 0.31g (8.16 mmol) of lithium aluminium hydride in 15 mL of ether (cooled to -20°C). After 20 min, at 20°C , ethyl acetate was slowly added to quench the hydride and the mixture was poured into ice-water. After stirring for 30 min the mixture was extracted with ether. The combined ether layers were washed with water and brine, and dried over sodium sulfate. Evaporation gave a colorless oil which was used without further purification. Yield. 2.32g (90%), $^1\text{H NMR}$ (CDCl_3) δ : 1.20(d, $J=6\text{Hz}$, CH), 2.28(q, $J=6\text{Hz}$, CH_2), 3.0(t, $J=6\text{Hz}$, OCH_2), 4.12(m, 1H), 5.47(m, 2H), 7.0-7.4 (m, 15H).

***N*-Alkylation of northebaine.** A solution of 0.17g (0.6 mmol) of northebaine, 0.15g (0.6 mmol) of iodo compound¹⁰ and 0.1g of potassium carbonate in 4 mL of acetonitrile was stirred at room temperature for 19h. Water and chloroform were added and the layers were separated. The aqueous layer was extracted with chloroform. The combined organic layers were washed with water and dried over sodium sulfate. Evaporation gave a residue which was chromatographed on silica gel using 2.5% methanol-chloroform as eluent and afforded 0.16g (66%) of the alkylated northebaine; $^1\text{H NMR}$ (CDCl_3) δ : 1.28(d, $J=6\text{Hz}$, 3H, CH_3) 2.00(s, 3H, COCH_3) 3.53(s, 3H, OCH_3) 3.78(s, 3H, OCH_3); IR (neat) 2830, 1730, 1600, 1230 cm^{-1} .

Dimethyl Acetylene Dicarboxylate-Thebaine (9). A solution of 8.8g (28.3 mmol) of thebaine and 3.51g (28.2 mmol) of dimethyl acetylenedicarboxylate in 75 mL of benzene was heated at 50°C for 1h, and allowed to cool to room temperature. After 24h, the crystals were filtered off and washed with benzene. The combined filtrates were condensed to 50 mL and the crystals were filtered off and washed with benzene. The crystalline adduct was air dried: yield 8.11g (71%); mp $138.5-142^{\circ}\text{C}$ (lit.¹⁶ $141-142^{\circ}\text{C}$); $^1\text{H NMR}$ (CDCl_3) 2.25 (s, 3H, NCH_3) 3.18(d, $J=19\text{Hz}$, 1H, $\text{C}_{10}\text{-H}_\alpha$) 3.52(s, 3H, OCH_3) 3.68(s, 1H, $\text{C}_5\text{-H}$) 5.48(d, $J=8\text{Hz}$, $\text{C}_{18}\text{-H}$) 6.18(d, $J=8\text{Hz}$, 1H, $\text{C}_{19}\text{-H}$) 6.48(d, $J=8\text{Hz}$, 1H, ArH) 6.61(d, $J=8\text{Hz}$, 1H, ArH).

Lactone(10). A solution of 3.0g (6.62 mmol) of adduct, 100 mL of ether and 100 mL of tetrahydrofuran was treated with 0.75g (18.7 mmol) of lithium aluminum hydride. The mixture was then added to 100 mL of 20% aqueous sodium hydroxide. The layers were separated and the aqueous layer was well extracted with chloroform. The combined organic layers were washed with water and dried over magnesium sulfate.

Evaporation and recrystallization from hexane gave a colorless crystalline solid: yield, 2.20g (84%) mp 245–248°C (lit.¹⁷ mp 249.5–250°C): ¹H NMR(CDCl₃) δ: 2.36(s, 3H, NCH₃) 3.53(s, 3H, OCH₃) 3.72(s, 3H, OCH₃) 3.8–4.2(m, 4H, C₂₀, 8, 9–H) 4.41(s, 1H, C₅-H) 5.42(d, J=8Hz, 1H, C₁₈-H) 5.86(d, J=8Hz, 1H, C₁₈-H) 6.47(d, J=9Hz, 1H, ArH) 6.60(d, J=9Hz, 1H, ArH).

Ester-Ether(11). A 0.1g (1.51 mmol) portion of crushed 85% potassium hydroxide pellet was added to a solution of 0.51g (1.28 mmol) of lactone in 11 mL of dioxane. The mixture was stirred at room temperature for 23h. Degreased potassium hydride (0.1g, 2.5 mmol) was added and the mixture stirred at room temperature for 1h. 6 mL (13.7g, 86 mmol) of methyl iodide was then added and the solution was stirred at room temperature for 6–12h. Water and chloroform were added and the layers were separated. The aqueous layer was extracted with chloroform. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to give an oil. The residue was chromatographed on silica gel using ether-hexane (3:2) as eluent to give ester-ether as a colorless solid: yield 0.38g (67%) ¹H NMR(CDCl₃) δ: 2.34(s, 3H, NCH₃) 3.13(s, 3H, OCH₃) 3.52(s, 3H, OCH₃) 3.62(s, 3H, COOCH₃) 3.79(s, 3H, OCH₃) 3.97(d, 1H, J=10Hz, C₈-H) 3.56(d, 1H, J=2Hz, C₅-H) 5.42(d, 1H, J=9Hz, C₁₈-H) 5.77(dd, 1H, J=2Hz, 9Hz, C₁₈-H) 6.46(d, 1H, J=9Hz, ArH), 6.50(d, 1H, J=9Hz, ArH) MS m/e (rel. intensity) 441(m⁺, 11) 382(11), 230(20), 43(100).

Nor-Ester-Ether(12). A solution of 0.5g (4.7 mmol) of cyanogen bromide in 4 mL of distilled chloroform was decanted from magnesium sulfate and added to 0.34g (0.70 mmol) of ester-ether. The solution was heated at reflux temperature for 3h, allowed to cool to room temperature, and evaporated at reduced pressure. A 20 mL portion of 3N aqueous hydrochloric acid was added and the mixture was heated at reflux temperature for 3h. The solution was allowed to cool to room temperature. After 1h, the solution was cooled to 0°C and aqueous sodium nitrite was added. After 15h at room temperature the solution was made basic with ammonium hydroxide and well extracted with chloroform. The combined chloroform layers were washed with water and dried over sodium sulfate. Evaporation and chromatography on silica gel using 60% ether-hexane as eluent afforded the nor-ester-ether as a colorless solid: yield 0.15g (50%), ¹H NMR(CDCl₃) δ: 3.08(s, 3H, CH₂OCH₃) 3.43(s, 3H, OCH₃) 3.53(s, 3H, COOCH₃); IR(neat), 3450, 2940, 1720, 1625, 1600, 750 cm⁻¹

Diester-Ether(13). Nor-ester-ether 0.22g (5 mmol) was treated with methyl bromo acetate 0.1g(6 mmol) in acetonitrile at reflux temperature for 5h. The solvent was evaporated. White solid diester-ether was obtained when the residue was purified by silica gel chromatography, using 30% ether in hex-

ane as eluent. ¹H NMR(CDCl₃) δ: 2.4(s, 2H, NCH₃) 3.13(s, 3H, OCH₃) 3.24(s, 3H, COOCH₃) 3.5(s, 3H, OCH₃) 3.6(s, 3H, COOCH₃) 3.78(s, 3H, OCH₃) 3.9(d, 1H, J=10Hz, C₈-H) 3.56(d, 1H, J=2Hz, C₅-H) 5.4(d, 1H, J=9Hz, C₁₈-H) 5.7(d, 1H, J=2Hz, C₁₈-H) 6.45(d, 1H, J=9Hz, ArH).

Ester-Ketone(14). By the Dieckman cyclization method, diester-ether 0.1g (0.2 mol) was treated with sodium methoxide in methanol. This was stirred for 3h at 0°C and quenched with distilled water. This solution was well extracted with chloroform. After purification by chromatography, colorless stout prism was obtained: yield 0.07 g(70%). ¹H NMR(CDCl₃) δ: 3.13(s, 3H, OCH₃) 3.5(s, 3H, OCH₃) 3.6(s, 3H, COOCH₃) 3.64(s, 3H, COOCH₃) 3.78(s, 3H, OCH₃) 3.92(d, 1H, J=10Hz, C₈-H) 3.56(d, 1H, J=2Hz, C₅-H) 5.42(d, 1H, J=9Hz, C₁₈-H) 5.7(d, 1H, J=2Hz, C₁₈-H) 6.45(d, 1H, J=9Hz, ArH). p 146°C

Acknowledgements. This work was supported, in part, by the Korean Science and Engineering Foundation. We are also greatly indebted to Dr. Rapoport for his many suggestions.

References

1. B.T. Belleau, F.R. Ahmod and A.D. Hardy, *J. Med. Chem.*, **17**, 807 (1974).
2. A.P. Feinberg, I. Greese and S.H. Sander, *Proc. Natl. Acad. Sci., USA* **71**, 4215 (1976).
3. K.W. Bentley and M.E. Hardy, *J. Am. Chem. Soc.*, **89**, 3267 (1967).
4. J.W. Lewis, M.J. Readhead, I.A. Selby, A.C.B. Smith and C.A. Young, *J. Chem. Soc.(C)*, 1158 (1971).
5. L.S. Schwab, *J. Med. Chem.*, **23**, 698 (1980).
S.N. Reameritz and A.R. Dershowitz, *J. Org. Chem.*, **22**, 44 (1957).
6. D. Sternbach and M. Shibuya, *Angew. Chem. Int. Ed. Engl.*, **18**, 634 (1979).
7. W.J. Batlman and H.N.O. Schmid, *Biochem. Biophysic. Acta.*, **144**, 355 (1967).
8. E.J. Corey and J.W. Suggs, *Tetrahedron Lett.* 2617 (1975).
9. M.E. Jung and M.A. Lyser, *J. Org. Chem.*, **42**, 3761 (1977).
10. G.A. Olah and S.C. Narang, *J. Org. Chem.*, **44**, 247 (1979).
11. J.W. Lewis and W.I. Rushworth, *J. Chem. Soc.*, 560 (1970).
12. T.R. Kelly, *Tetrahedron Lett.*, 3859 (1977).
13. M. Meerwein, *Chem. Ber.* **89**, 2060 (1956).
14. W.J. Baumann and H.N.O. Schmid, *Biochem. Biophys. Acta.*, **144**, 365 (1967).
15. D. Sternbach and M.A. Shihya, *Angew. Chem. Int. Ed. Engl.*, **19**, 320 (1980).
16. K.W. Bentley and D.G. Hardy, *J. Am. Chem. Soc.*, **89**, 3281 (1967).