tography using a ether-hexane mixture as the eluent. The two major fractions contained 2-methyl-3-cyanopyrrole (**7**) and 2-methyl-4-cyanopyrrole (**10**), respectively. The ratio of the two isomers (1:1) was determined by VPC analysis (5% SE-30) after DDQ oxidation. The spectral properties of the two materials were identical with authentic samples.

Irradiation of Diazirine in Acetonitrile in the Presence of Methyl Acrylate. The experimental procedure used was the same as that described for the reaction of diazirine in acetonitrile in the presence of acrylonitrile. The ratio of the two cyclic regioisomers **4** and **5** obtained after DDQ oxidation was 1:1.

Irradiation of Diazirine in Acetonitrile in the Presence of Methyl Propiolate. The experimental procedure used was the same as described for the reaction of diazirine in acetonitrile in the presence of dimethyl acetylenedicarboxylate. The ratio of the two cycloaddition products **4** and **5** was 1:1.

Acknowledgment. A. P. and N.J.T. acknowledge the National Science Foundation for their generous support of this research. N.J.T. thanks the Air Force Office of Scientific Research for its support of this research.

Registry No. 1, 103852-58-0; **2**, 98587-57-6; **3**, 90610-59-6; **4**, 3168-85-2; **5**, 40611-76-5; **7**, 26187-27-9; **10**, 42046-60-6; **24**, 98587-59-8; **25**, 103852-60-4; *trans*-**26**, 59790-39-5; *cis*-**26**, 59790-38-4; **27**, 101402-41-9; **30**, 98587-60-1; **31**, 66614-71-9; **32**, 3306-05-6; **33**, 7568-93-6; **35**, 42794-92-3; $CH_2{=}N_2$, 334-88-3; CH_3CN, 75-05-8; diazirine, 157-22-2; (*p*-tolylsulfonyl)methyl isocyanide, 10564-55-3; 1-((methylisocyanomethyl)sulfonyl)-4-methylbenzene, 81993-07-9; maleic anhydride, 108-31-6; fumaronitrile, 764-42-1; diethyl fumarate, 623-91-6; dimethyl acetylenedicarboxylate, 762-42-5; diethyl maleate, 141-05-9; benzaldehyde, 100-52-7; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; methyl propiolate, 922-67-8; (trimethylsilyl)methyl triflate, 64035-64-9.

Polyene Cyclization Strategy in the Stereospecific Synthesis of *B/C-trans*-Morphinan. A Total Synthesis of (±)-*O*-Methylpallidinine

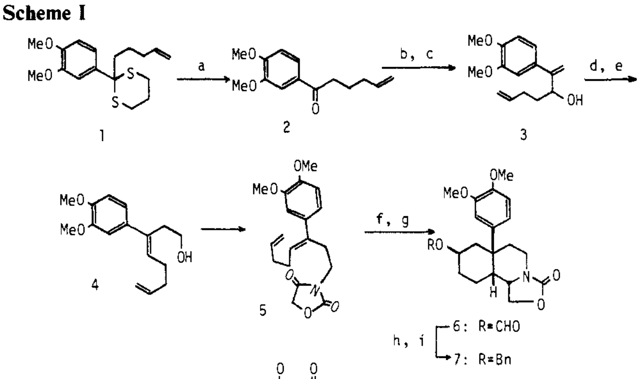
Shinzo Kano,* Tsutomu Yokomatsu, Hajime Nemoto, and Shiroshi Shibuya

Contribution from the Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan. *Received March 10, 1986. Revised Manuscript Received June 9, 1986*

Abstract: Reduction of the oxazolidine-2,4-dione **5** with $NaBH_4$ followed by cyclization with formic acid gave the 6a-aryloxazoloisoquinolin-8-formate **6** with stereospecificity. A stereospecific synthesis of 6-hydroxy-*B/C-trans*-morphinan **15** was achieved from **5**. Oxidation of **15** yielded the 6-oxo-*B/C-trans*-morphinan **16** which constituted a formal total synthesis of (±)-*O*-methylpallidinine.

The field of biomimetic cationic polyene cyclization has been used in the synthesis of complex multicyclic compounds with excellent stereocontrol.[1,2] Polyene cyclization by the use of *N*-acyliminium ion as a cationic initiating center[3,4] has also been applied to a synthesis of some azapolycyclic systems.[5] The results[6] from our laboratory have demonstrated that *N*-acyliminium ion-induced polyene cyclization provided an efficient route to *cis*-4a-aryldecahydroisoquinolin-6-ols with stereospecificity. A-strain[7] caused by phenyl and butenyl side chains in the benzylcationic intermediates was found to be significant to control the stereochemical course of this cyclization.[6] In view of the large amount of work on a synthesis of morphine-based structural variants,[8] a synthesis of 6-oxygenated *B/C-trans*-morphinan derivatives has been of considerable interest from both synthetic and medicinal points of view.[9] Furthermore, 6-oxo-*B/C-trans*-morphinan can be easily convertible to B/C-cis isomer by known chemistry.[10] Our interest in a synthetic effort to create routes

Scheme I



Reagent: (a) CuO, $CuCl_2$; (b) $PhS(O)CH_2P(O)(OEt)_2$; (c) DBU; (d) KH, $n\text{-}Bu_3SnCH_2I$; (e) n-BuLi; (f) $NaBH_4$; (g) HCOOH; (h) NaOH; (i) $C_6H_5CH_2Br$

(1) (a) Reviews on polyene cyclization; Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Bartlett, P. A. *Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341-409.

(2) (a) Groen, M. B.; Zeelen, F. *J. Org. Chem.* **1978**, *43*, 1961. (b) Peters, J. A. M.; Posthumus, T. A. P.; van Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *J. Org. Chem.* **1980**, *45*, 2208. (c) Johnson, W. S.; Brener, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J. *J. Am. Chem. Soc.* **1982**, *104*, 3508. (d) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522 and references cited therein.

(3) For reviews: (a) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. (b) Speckamp, W. N. *Tetrahedron* **1985**, *41*, 4367.

(4) (a) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576. (b) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555. (c) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (d) Wijinberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. (e) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3811. (f) Nossin, P. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3207. (g) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (h) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(5) (a) Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 173. (b) Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 935.

(6) Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *J. Org. Chem.* **1985**, *50*, 3449.

(7) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(8) (a) Johnson, M. R.; Milne, G. M. In *Burger's Medicinal Chemistry*, 4th ed.; Wolf, M., Ed.; Wiley: New York, 1981; Part 3, p 689. (b) Palmer, D. C.; Straus, M. J. *Chem. Rev.* **1977**, *77*, 1. (c) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650. (d) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485. (e) Evans, D. A.; Mitsch, C. H.; Thomas, R.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. (f) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064. (g) Evans, D. A.; Mitsch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285. (h) Shenvy, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942.

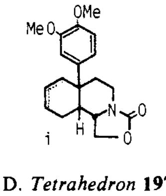
(9) (a) Schmidhammer, H.; Jacobson, A. E.; Brossi, A. *Med. Res. Rev.* **1983**, *3*, 1. (b) Fujii, I.; Abe, M.; Hayakawa, K.; Kanematsu, K. *Chem. Pharm. Bull.* **1984**, *32*, 4670.

fundamentally new and different from those led us to develop our previous work[6] to a stereospecific synthesis of 6-oxygenated *B/C-trans*-morphine ring system. We now describe a concepturally new and stereospecific method leading to 6-hydroxy- and 6-oxo-*B/C-trans*-morphinan, which accomplishes a formal total synthesis of (±)-*O*-methylpallidinine (**17**).[11]

(3*E*)-3,7-Octadien-1-ol **4**, required for a synthesis of *N*-acyliminium ion–polyene system,[12] was prepared stereospecifically as outlined in Scheme I. Pentenylation of 2-(3′,4′-dimethoxyphenyl)-1,3-thiane (*n*-BuLi, THF, −25 to 20 °C and 4-pentenyl-1-benzenesulfonate)[13] afforded **1** (100%, oil). Decomposition of **1** (CuO, $CuCl_2$, acetone, 20 °C), followed by vinylsulfinylation ($PhSOCH_2PO(OEt)_2$, *n*-BuLi, THF) and subsequent treatment with diazabicyclo[5.4.0]undecene (DBU) in toluene (reflux) gave **3** (65% yield from **2**, oil) through [2,3]-sigmatropic rearrangement of allyl sulfoxide[14] formed in situ. 3,7-Octadien-1-ol synthesis incorporating *E* oriented double bond was successfully achieved according to Still's method.[15] (Tri-*n*-butylstannyl)methylation of **3**, followed by metal exchange (*n*-BuLi) yielded **4** as a single product without formation of *Z* isomer. Condensation of **4** with oxazolidin-2,4-dione by Mitsunobu's method[16] gave **5** (99% yield, oil). Reduction of **5** ($NaBH_4$), followed by cyclization with formic acid afforded **6**.[17] Hydrolysis of **6** (MeOH/3 N NaOH, room temperature), followed by benzylation (NaH, THF/DMF, $C_6H_5CH_2Br$, 18-crown-6) yielded **7** (82.8% yield, mp 115–117 °C).

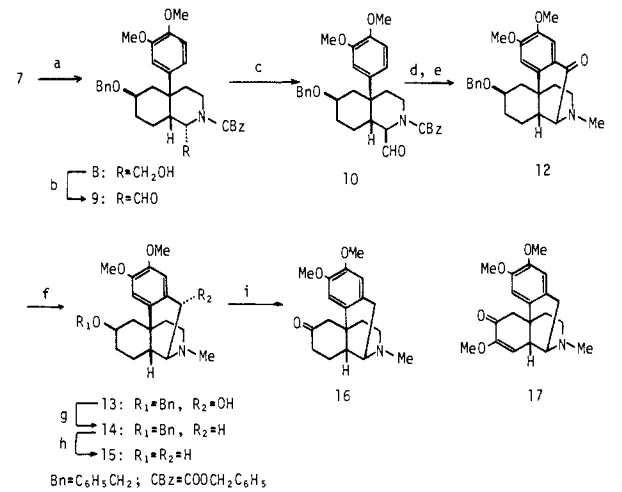
Conversion of **7** to **9** was effected by ring cleavage of **7** (8% EtOH–KOH, reflux), followed by carbobenzylation and subsequent Swern oxidation[18] of **8**. For a preparation of *B/C-trans*-morphinan, epimerization at 1-position is the essential problem to be solved to cyclize at 6′-position.[19] Considering the significantly severe A-strain[7] caused by N–CO– and 1-CHO (see **11a**), it is conceivable that epimerization of **9** to the thermodynamically more stable isomer **10** is feasible. Apparently, this A-strain assisted epimerization proceeded through enolation and concomitant protonation procedure.[20] Surprisingly, protonation occurred from the more hindered side to give the thermodynamically more favorable isomer. Although it is known that A-strain can pit against considerably severe 1,3-interaction,[7] the epimerization product seems to be stabilized by a formation of π-stacking[21] between the benzene ring and carbonyl. Two sets of characteristic signals observed in its ^1H NMR spectrum might indicate the presence of two π-stacking models as **11b,c** (partial structures). Cyclization of **10**, followed by Jones oxidation yielded **12**. Reduction of **12** ($LiAlH_4$, THF), followed by reductive dehydration of **13** (Et_3Si, 1:1 CH_2Cl_2/CF_3COOH, 55 °C), gave **14**. Catalytic hydrogenation of **14** gave **15**. For the verification of the ring juncture, **15** was subjected to oxidation (*t*-BuOK, benzophenone) to give **16**,

(10) Gate, M.; Helg, R. *J. Am. Chem. Soc.* **1956**, *78*, 1380.
(11) McMurry, J. E.; Fariana, V. *Tetrahedron Lett.* **1983**, *24*, 4653.
(12) Cyclization of the iminium ion derived from (3*Z*)-isomer of **5** gave the trans fused isoquinoline but in very poor yield.
(13) (a) Seebach, D.; Corey, E. *J. Org. Chem.* **1975**, *40*, 231. (b) Seebach, D.; Wilkam, E.-M. *Synthesis* **1976**, 476.
(14) Hoffmann, R. W.; Goldmann, S.; Maak, N.; Gerlach, R.; Frickel, F.; Steinbach, G. *Chem. Ber.* **1980**, *113*, 819.
(15) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.
(16) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(17) In this cyclization reaction, formation of **i** was accompanied (10% yield, oil). **6** and **i** were easily separated by column chromatography on silica gel (AcOEt/hexane, 3:1).

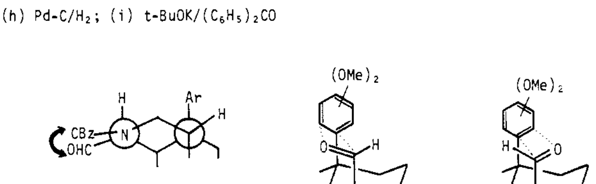


(18) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(19) Any attempts to cyclize **9** were not successful.
(20) Application and limitation of this A-strain-assisted isomerization is under investigation by using similar chemical systems to **9**.
(21) (a) Trost, B. M.; O'Kronly, D.; Genet, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7595. (b) Oppolozer, W.; Kurth, M.; Reichkin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802.

Scheme II



Reagent: (a) EtOH-KOH, $ClCOOCH_2C_6H_5$; (b) Me_2SO, $(COCl)_2$, Et_3N; (c) t-BuOK; (d) $BF_3\ Et_2O$; (e) Jones reagent; (f) $LiAlH_4$; (g) Et_3SiH/CF_3COOH; (h) Pd-C/H_2; (i) t-BuOK/$(C_6H_5)_2CO$



11a 11b 11c

the structure of which was confirmed by comparison of its ^1H NMR ($CDCl_3$, 400 MHz) with that of the authentic specimen[11] kindly donated from Professor John E. McMurry, Cornell University. Since transformation of **16** to (±)-*O*-methylpallidinine was already accomplished through the 6,7-dioxo derivative, a synthesis of **16** in this work constitutes a formal total synthesis of (±)-*O*-methylpallidinine. The stereospecific synthesis 6-hydroxy-*B/C-trans*-morphinan system achieved by an application of polyene cyclization would be widely applicable to a synthesis of a variety of morphine analogues. (See Scheme II).

Experimental Section

***E*-3-(3′,4′-Dimethoxyphenyl)-3,7-octadien-1-ol (4).** To a stirred suspension of KH (0.68 g, 16.9 mmol) in THF (25 mL) was added a solution of **3** (2.1 g, 8.5 mmol) in THF (25 mL) under ice-cooling. To this solution was added a solution of (tributylstannyl)methyl iodide (4.2 g, 10.2 mmol) in THF (20 mL) under stirring at the same temperature. After the stirring had been continued at the same temperature for 1.5 h, excess KH was decomposed with MeOH and poured onto water and extracted with $CHCl_3$. The extract was worked up, and the remaining residue was chromatographed on silica gel. Elution with hexane–Et_2O (9:1) gave the (tributylstannyl)methyl ether (3.9 g, 83.4% yield) as a colorless oil. To a solution of this oil in THF (70 mL) was added *n*-BuLi (8.8 mL of 1.6 M hexane solution, 14 mmol) at −78 °C. After the stirring had been continued for 0.5 h at the same temperature and for 10 min at room temperature, the mixture was poured onto water and extracted with $CHCl_3$. The extract was worked up to give **4** (643 mg, 94.3% yield) as an oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.94 (1 H, dd, *J* = 2, 9 Hz), 6.81 (1 H, d, *J* = 9 Hz), 6.14–5.61 (1 H, m), 5.75 (1 H, t, *J* = 7 Hz), 5.21–4.91 (2 H, m), 3.87 (3 H, s), 3.83 (3 H, s), 3.60 (2 H, t, *J* = 6 Hz), 2.27 (4 H, m); MS, *m/e* (rel intensity) 262 (M^+, 60), 221 (100); exact MS calcd for $C_{16}H_{22}O_3$ 262.1567, found 262.1556; IR ($CHCl_3$) 3670, 3600, 1630 cm^{-1}.

6a-(3′,4′-Dimethoxyphenyl)oxazololsoquinolin-8-formate (6). To a stirred solution of **5** (750 mg, 2.2 mmol) in MeOH (15 mL) was added $NaBH_4$ (450 mg, 12.1 mmol) under ice-cooling. After the stirring had been continued for 10 min at the same temperature, excess $NaBH_4$ was decomposed with acetone. The solvent was evaporated, and the resulting residue was diluted with water and extracted with $CHCl_3$. The extract was worked up. A mixture of the remaining residue and formic acid (4.4 mL) was stirred at room temperature for 3 h. The mixture was made basic with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was worked up, and the resulting residue was chromatographed on silica gel. Elution with AcOEt–hexane (2:1) yielded **6**[16] (632 mg, 76.7% yield), mp

160–162 °C (MeOH-Et_2O): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (1 H, s), 6.91 (1 H, dd, J = 2.2, 8.5 Hz), 6.88 (1 H, d, J = 8.5 Hz), 6.85 (1 H, d, J = 8.5 Hz), 5.12 (1 H, m, $W_{1/2}$ = 20 Hz), 4.20 (1 H, dd, J = 8.8, 8.8 Hz), 4.14 (1 H, dd, J = 4.5, 8.8 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 3.12 (1 H, ddd, J = 3.6, 13, 13 Hz); MS, m/e (rel intensity) 375 (M^+, 30), 191 (100); IR ($CHCl_3$) 1740, 1715 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.75. Found: C, 63.77; H, 6.79; N, 3.82.

***B/C-trans*-Morphinan 12.** To a stirred solution of **9** (550 mg, 1.0 mmol) in Et_2O (15 mL) was added t-BuOK (111 mg, 1.0 mmol) at −25 °C. After the stirring had been continued at the same temperature for 2 h, the mixture was diluted with aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was worked up to give **10** (430 mg, 79.2% yield) [^1H NMR ($CDCl_3$) δ 8.89 (0.6 H, s), 8.86 (0.4 H, s), 7.31 (4 H, s), 7.26 (6 H, s), 6.78 (3 H, br s), 5.08 (1.2 H, s), 5.03 (0.8 H, s), 4.47 (2 H, s), 3.88 (6 H, br s); MS, m/e (rel intensity) 543 (M^+)]; this was used for the following reaction without further purification, since it is sensitive to air. To a stirred solution of **10** (430 mg, 0.79 mmol) in toluene (10 mL) was added $BF_3 \cdot Et_2O$ (168 mg, 1.18 mmol) at −15 °C. After 0.5 h, the mixture was diluted with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was worked up. To a stirred solution of the resulting residue in acetone (10 mL) was added Jones reagent (0.5 mL) under ice-cooling. After 5 min, excess reagent was decomposed with isopropyl alcohol. The mixture was made basic with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was worked up, and the remaining residue was chromatographed on silica gel. Elution with hexane–AcOEt (3:1) gave **12** (210 mg, 49.1% yield) as an uncrystallized powder: ^1H ($CDCl_3$, 400 MHz) δ 7.54 (5 H, s), 7.35 (10 H, m), 6.77 (1 H, s), 5.17 (2 H, m), 5.85 (1 H, br s), 4.70 (2 H, d, J = 11.8 Hz), 4.56 (2 H, d, J = 11.8 Hz), 3.94 (3 H, s), 3.92 (3 H, s), 3.76 (1 H, m), $W_{1/2}$ = 24.8 Hz); MS, m/e 541 (M^+); exact MS calcd for $C_{33}H_{35}NO_6$ 541.2462, found 541.2506; IR ($CHCl_3$) 1690 cm^{-1}.

6-Hydroxy-*B/C-trans*-morphinan 15. A mixture of **14** (100 mg, 0.25 mmol), EtOH (10 mL), 12 N HCl (3 drops), and 10% Pd–C (100 mg) was stirred under the atmospheric pressure of H_2 at room temperature for 16 h. After removal of the catalyst by filtration, the solvent was evaporated. The resulting residue was dissolved in 1 N HCl and washed with Et_2O. The aqueous layer was made basic with 28% ammonia and extracted with $CHCl_3$. The extract was worked up and the resulting residue was chromatographed on silica gel. Elution with $CHCl_3$–isopropyl alcohol–28% ammonia (50:5:1) gave **15** (67.4 mg, 85% yield), mp 145–147 °C (Et_2O–hexane): ^1H NMR ($CDCl_3$, 400 MHz), δ 6.78 (1 H, s), 6.63 (1 H, s), 4.03 (1 H, m), 3.85 (3 H, s), 3.84 (3 H, s), 3.11 (1 H, d, J = 17.8 Hz), 2.90 (1 H, d, J = 5.2 Hz), 2.65 (1 H, dd, J = 5.2, 17.8 Hz), 2.34 (3 H, s); MS, m/e (rel intensity) 317 (M^+, 80), 166 (100); IR ($CHCl_3$) 3670, 3600, 1610, 1510, 1460 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.55; H, 8.65; N, 4.27.

6-Oxo-*B/C-trans*-morphinan 16. A mixture of **15** (63.6 mg, 0.20 mmol), t-BuOK (67.5 mg, 0.60 mmol), benzophenone (367 mg, 2.0 mmol), and benzene (5 mL) was heated under reflux for 6 h. The mixture was diluted with benzene and extracted with 1 N HCl. The acidic layer was made basic with 28% ammonia and extracted with $CHCl_3$. The extract was worked up to give **16** (50 mg, 80% yield) the ^1H NMR ($CDCl_3$, 400 MHz) spectrum of which was identical with that donated from Professor John E. McMurry; MS, m/e (rel intensity) 315 (M^+, 100), 300 (30), 271 (50), 258 (60), 244 (30), 201 (10), 164 (70), 122 (40).

Acknowledgment. We are grateful to Professor John E. McMurry for the generous gifts of ^1H NMR and ^{13}C NMR spectra of authentic sample of 6-oxo-*B/C-trans*-morphinan **16**.

Registry No. 1, 104072-34-6; **2**, 104072-35-7; (±)-**3**, 104072-36-8; (±)-**3** (tributylstannyl)methyl ether, 104072-44-8; **4**, 104072-37-9; **5**, 104072-38-0; (±)-**6**, 104072-39-1; (±)-**7**, 104072-40-4; (±)-**8**, 104072-41-5; (±)-**9**, 104072-42-6; (±)-**10**, 104072-43-7; (±)-**12**, 104072-45-9; (±)-**13**, 104072-46-0; (±)-**14**, 104072-47-1; (±)-**15**, 104072-48-2; (±)-**16**, 104112-75-6; (±)-**17**, 88199-99-9; oxazolidin-2,4-dione, 2346-26-1.

Supplementary Material Available: Experimental details for a synthesis of **1**, **2**, **3**, **5**, **7**, **8**, **9**, **13**, and **14** and ^1H NMR ($CDCl_3$, 400 MHz) spectral chart on **16** (7 pages). Ordering information is given on any current masthead page.

Fragmentations and Rearrangements in Organic Synthesis

James B. Hendrickson

Contribution from the Edison Chemical Laboratories, Brandeis University, Waltham, Massachusetts 02254. *Received March 28, 1986*

Abstract: The families of fragmentation and skeletal rearrangement reactions are described and generalized so as to incorporate all variations. This then affords a simple systematic protocol for retrosynthetic mapping of all possible fragmentations and rearrangements onto a target skeleton. The number of such mapping modes suggests that without such a system synthesis planning can easily miss some profitable paths.

In previous discussions of systematic synthesis design,[1] we have focused solely on pathways involving sequential construction reactions and the generation of bondsets to indicate which skeletal bonds to construct. However, many successful short syntheses actually break carbon–carbon bonds as well as construct them. The purpose of the present paper is to explore ways to incorporate such fragmentations efficiently and comprehensively into synthesis design. In principle cleavage of carbon–carbon bonds is retrograde since, in the synthesis of a large target molecule from small starting material pieces, it is only construction reactions which are obligatory. Hence for an efficient synthesis there must be special and compelling reasons for using fragmentation reactions. This probably accounts for the observation that relatively little study of fragmentations appears in the synthesis literature.

In retrosynthetic analysis of a target skeleton, we delete skeletal bonds in determining which bonds are to be constructed, and this analysis is central to our previous discussions.[1] In seeking carbon–carbon cleavages, or fragmentations, we must add to the skeleton those bonds which are to be broken in the synthesis. Each such addition affords a new target to be dissected in the normal way for construction from smaller starting materials. Since there are so many ways to add new bonds to a skeleton,[2] it is imperative to limit the number of elected fragmentations severely and therefore to provide stringent criteria for assessing profitable ones.

(1) (a) Hendrickson, J. B.; Braun-Keller, E.; Toczko, A. G. *Tetrahedron, Suppl.* **1981**, *No. 1*, **37**, 359. (b) Hendrickson, J. B.; Grier, D. L.; Toczko, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5228.

(2) The number of ways to add one bond to a skeleton of n atoms, r rings, and q quaternary atoms equals the combinations of $(n - q)$ atoms two at a time minus existing bonds + $4q$, or $N = {}^1/_2[n(n-3) + q(q - 2n + 9)] - r + 1$. For a bicyclic sequiterpene (n = 15) with one quaternary carbon there are 79 ways to add one more bond.

0002-7863/86/1508-6748$01.50/0