Table IV. Fluorination Conditions for Tetra-*n*-propyl Orthocarbonate

He, cm^3 min^{-1}	F_2, cm^3 min^{-1}	temp, °C	time, days
100	1	-100	1
100	1	-90	1
100	1	-80	1
50	1	-80	1
50	2	-80	1
20	2	-80	1
20	4	-60	1
10	4	-60	1
0	4	-30	1
0	4	rt	1
0	4	50	1
60	0	50	0.5

Perfluorotetra-*n*-propyl orthocarbonate: bp 132 °C. IR analysis (thin film, KBr): 1343 (m), 1243 (vs, br), 1204 (vs), 1140 (s), 1101 (s), 994 (s), 753 (m) cm^{-1}. MS analysis: *m/e* 567 ($M - C_3F_7O)^+$, 548 $(C_{10}F_{20}O_3)^+$, 401 $[CF(OC_3F_7)]^+$, 400 $(C_8F_{16})^+$, 382 $(C_7F_{14}O_2)^+$, 235 $(C_4F_9O)^+$, 213 $(C_4F_7O_2)^+$, 169 $(C_3F_7^+$, base peak), 119 $(C_2F_5)^+$, 100 $(C_2F_4)^+$, 69 $(CF_3)^+$, 47 $(CFO)^+$. ^{19}F NMR analysis: $\delta(CFCl_3)$ - 82.2 (CF_3), -85.5 (-OCF_2-), and -131.0 (-CF_2-). Anal. Calcd for $C_{13}F_{28}O_4$: C, 20.76; F, 70.73. Found: C, 20.51; F, 70.46.

Acknowledgment. We are grateful for support of this work by the NASA Lewis Research Center (NAG3-602) and the Air Force Office of Scientific Research (AFOSR-88-0084).

Registry No. $C(OCH_3)_4$, 1850-14-2; $C(OC_2H_5)_4$, 78-09-1; $C(OCF_3)_4$, 92639-87-7; $C(OC_2F_5)_4$, 118631-42-8; $C(OC_6H_7)_4$, 597-72-8; $C(OC_6F_7)_4$, 118631-43-9.

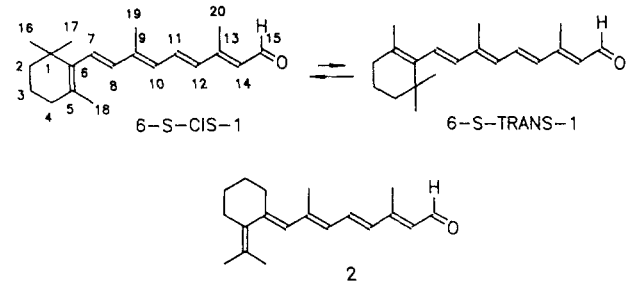
Reactions of Vinylogous Phosphonate Carbanions and Reformatsky Reagents with a Sterically Hindered Ketone and Enone

Cynthia Y. Robinson, Wayne J. Brouillette,* and Donald D. Muccio*

Department of Chemistry, University of Alabama at Birmingham, Birmingham, Alabama 35294

Received September 27, 1988

All *trans*-retinal (vitamin A aldehyde, 1) occurs in solution as a mixture of nearly planar 6-*s*-*trans* and distorted 6-*s*-*cis* conformations, with the latter predominating.[1,2] However, only one of these conformations is incorporated into retinal-protein complexes such as the visual pigment rhodopsin[3,4] and the highly studied analogue bacteriorhodopsin.[5-7] In order to further study the interactions of specific 6-s conformations of retinal with these proteins, we proposed the synthesis of a conformationally defined, distorted 6-*s*-*cis* analogue (2) of retinal. This analogue contains the same steric interaction that results in nonplanarity of the 6-*s*-*cis* conformation in retinal, namely that between the 18-methyl and 8-hydrogen.



We envisioned that the synthesis of 2 could be accomplished from the aldehyde derivative of 3 (Scheme I) by a Horner-Emmons condensation, which has been commonly employed in retinoid syntheses by others[8] as well as in our laboratory.[9] It was proposed that intermediate 3 could be prepared via an olefination of 2-isopropylidenecyclohexanone (5, Scheme I). However, our attempts to convert 5 to 3 by a Horner-Emmons condensation failed, and model reactions suggested that this was due to unfavorable steric and electronic effects. We then attempted a Reformatsky reaction, but the product obtained was the unprecedented (2*Z*,4*E*)-carboxylic acid 8 (Scheme I). We further investigated this Reformatsky reaction and here report a study of the reactions between two stereochemically defined vinylogous Reformatsky reagents and a sterically hindered ketone and enone. The results suggest that δ-lactone formation is required for the successful addition of vinylogous Reformatsky reagents to ketones in the presence of unfavorable steric and electronic effects and that vinylogous Reformatsky reagents likely stereomutate via s-cis, s-trans isomerization of the zinc dienolate during reversible addition to the ketone.

Results and Discussion

The first approach to unsaturated ester 3 involved a Horner-Emmons condensation between 4 and 5 (Scheme I), since we and others have previously employed this procedure in the preparation of retinoids from α,β-unsaturated ketones.[8,9] However, enone 5 was found to be unreactive under these conditions, which, as shown by the study summarized in Table I, is due to steric and electronic effects in both the ketone and phosphonate ester.

As shown in Scheme I, the next approach to 3 involved a Reformatsky reaction between 5 and vinylogous bromo ester 6 (as an isomeric mixture containing 65% *E* and 35% *Z* configurations). It was anticipated that this reaction would yield the normal hydroxy ester product 7 (Scheme I), but the only product isolated was the unprecedented carboxylic acid 8. The configuration of 8 was determined to be 2*Z*,4*E* by a study of the nuclear Overhauser effect (NOE) between the methyl protons and neighboring vinyl protons. Irradiation of the 3-methyl protons produced a large NOE to H-2 (27% enhancement), consistent with those reported for similar studies with crotonaldehyde and 9-*cis*- and 13-*cis*-retinal;[10,11] this established the 2*Z* configuration. The large NOE observed for H-4 (20% enhancement) when the H-9 methyl protons were irradiated likewise established the 4*E* configuration, while only small NOE values (4-6% enhancement) were observed when the H-8 methyl group was irradiated.

Except for the use of *tert*-butyl ester Reformatsky reagents,[12] Reformatsky reactions have not been reported

(1) Honig, B.; Hudson, B.; Sykes, B. D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1289.
(2) Honig, B.; Warshel, A.; Karplus, M. *Acc. Chem. Res.* **1975**, *8*, 92.
(3) Mollevanger, L.; Kentgens, A.; Pardoen, J.; Courtin, J.; Veeman, W.; Lugtenburg, J.; Grip, W. *Eur. J. Biochem.* **1987**, *163*, 9.
(4) Smith, S.; Palings, I.; Copie, V.; Raleigh, D.; Courtin, J.; Pardoen, J.; Lugtenburg, J.; Mathies, R.; Griffin, R. *Biochemistry* **1987**, *26*, 1606.
(5) van der Steen, R.; Biesheuvel, P. L.; Mathies, R. L.; Lugtenburg, J. *J. Am. Chem. Soc.* **1986**, *108*, 6410.
(6) Harbison, G. S.; Smith, S. O.; Pardoen, J. A.; Courtin, J. M. L.; Lugtenburg, J.; Herzfeld, J.; Mathies, R. A.; Griffin, R. G. *Biochemistry* **1985**, *24*, 6955.
(7) Rodman Gilson, H. S.; Honig, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 1943.
(8) Isler, O. *Carotenoids*; Birkhäuser Verlag: Basel, 1971.
(9) Vaezi, M. F.; Robinson, C. Y.; Hope, K. D.; Brouillette, W. J.; Muccio, D. D. *Org. Prep. Proc. Int.* **1987**, *19*, 187.
(10) Rowan, R. III; McCammon, J. A.; Sykes, B. D. *J. Am. Chem. Soc.* **1974**, *96*, 4773.
(11) Rowan, R. III; Sykes, B. D. *J. Am. Chem. Soc.* **1974**, *97*, 1023.

0022-3263/89/1954-1992$01.50/0

Scheme I

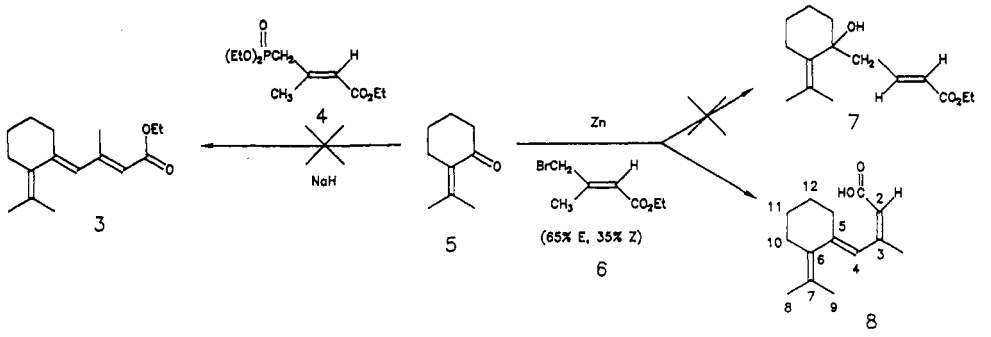
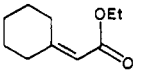
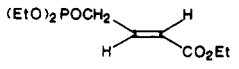
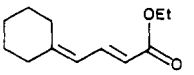
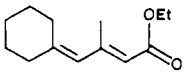
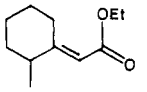
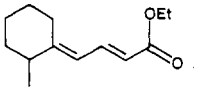
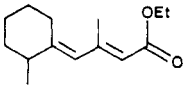
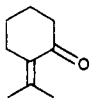


Table I. Horner-Emmons Reactions

ketone	phosphonate ester	product	isolated % yield[a]
 9	$(EtO)_2POCH_2CO_2Et$ 10	 11	74[b]
9	 12	 13	32
9	4	 14	28
 15	10	 16	55[c]
15	12	 17	21
15	4	 18	10
 5	4 or 10	–	0

[a] Yields do not reflect recovered starting ketone and are based upon products isolated from preparative TLC. [b] Literature[26] yield 70%. [c] Literature [27] yield 71%.

to directly produce (without subsequent hydrolysis) carboxylic acid products. A recent report[13] described the reaction between α,β-unsaturated ketones (nonhindered) and vinylogous Reformatsky reagents, but the observed products were the expected 1,2- and 1,4-addition products resulting from either α- or γ-attack by the Reformatsky reagent. The only literature precedent for the 2*Z* configuration of **8** concerned the δ-lactone products formed when vinylogous Reformatsky reagents were reacted with hindered aldehydes or benzaldehyde[14-16] or an acyclic ketone.[17] (γ-Lactones have been reported[18,19] to result via a different mechanism.) This suggests a δ-lactone as an intermediate in the formation of **8**, which under the conditions of the reaction presumably undergoes eliminative ring opening by ethoxide.

These observations led us to further investigate the Reformatsky reaction that produced product **8**. In particular, we wished to study the effect of configuration of the vinylogous Reformatsky reagent on the outcome of the reaction, since only the *Z* Reformatsky reagent (or an intermediate where the carbon–carbon double bond contributed by the Reformatsky reagent has stereomutated to the *Z* configuration) can produce the observed product. Also, we wished to investigate the effect of steric hindrance in both the ketone and Reformatsky reagent.

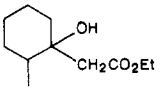
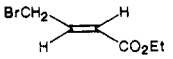
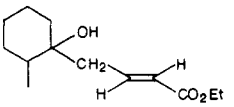
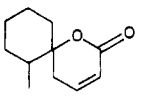
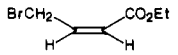
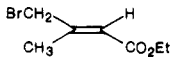
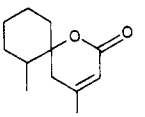
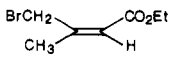
A previous study[14] demonstrated that the Reformatsky reactions of pure (*E*)- or (*Z*)-methyl 4-bromo-3-methyl-2-butenoate with hindered aldehydes gave identical δ-lactone products, although the use of pure (*E*)-ethyl 4-bromo-2-butenoate (**21**) in the Reformatsky reaction was reported[13,20] to only give products with the *E* stereochemistry conserved. Stereomutation of the former vinylogous Reformatsky reagent could reasonably occur by either an s-trans to s-cis equilibration of the zinc dienolate or an intermolecular allylic hydrogen transfer. The lack of stereomutated products with the vinylogous Reformatsky reagent derived from **21**, in fact, suggested that the allylic hydrogen transfer mechanism was more likely. In order to attempt to distinguish between these possibilities, the stereochemistry of Reformatsky reactions involving the *E* or *Z* isomer of bromo ester **21** as well as bromo ester **6** were investigated. It was of particular interest to determine if (*Z*)-**21**, which has not previously been utilized in Reformatsky reactions and is incapable of stereomutating via allylic hydrogen transfer, would provide enhanced yields of products containing the *Z* stereochemistry.

The studies that were performed to address these questions are summarized in Tables II and III, which compare identical Reformatsky reactions of 2-methylcyclohexanone (**15**) and 2-isopropylidenecyclohexanone (**5**), respectively. In this study all Reformatsky reactions were carried out under conditions reported[13,20] to give γ-addition of vinylogous Reformatsky reagents to simple ketones.

The results in Tables II and III reveal the sensitivity of the Reformatsky reaction to steric and electronic effects. As anticipated, enone **5** was considerably less reactive than ketone **15** toward 1,2-addition. One unexpected result was that enone **5**, despite its low reactivity, in the reaction with

(12) Cornforth, D. A.; Opara, A. E.; Read, G. *J. Chem. Soc. C* **1969**, 2799.
(13) Hudlicky, T.; Natchus, M. G.; Kwart, L. D.; Colwell, B. L. *J. Org. Chem.* **1985**, *50*, 4300.
(14) Gedye, R. N.; Arora, P.; Khalil, A. H. *Can. J. Chem.* **1975**, *53*, 1943.
(15) Harper, S. H.; Oughton, J. F. *Chem. Ind.* **1950**, 574.
(16) Fuson, R.; Southwick, P. L. *J. Am. Chem. Soc.* **1944**, *66*, 679.
(17) Eiter, K.; Truscheit, E.; Oediger, H. *Angew. Chem.* **1960**, *732*, 948.
(18) Short, R. P.; Hudlicky, T. *J. Org. Chem.* **1982**, *47*, 1522.
(19) Rosowsky, A.; Papthanasopoulos, N.; Lazarus, H.; Foley, G. E.; Modest, E. J. *J. Med. Chem.* **1974**, *17*, 672.
(20) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845.

Table II. Reformatsky Reactions of Ketone 15

ketone	bromo ester	product	isolated % yield[a]	product composition,[b] %
	$BrCH_2CO_2Et$ **19**		70[c]	–
15		**20**		
15	 (*E*)-**21**	 **22** +  **23**	40 (mixture)	62 38
15	 (*Z*)-**21**	**22** + **23**	12 (mixture)	74 26
15	 (*E*)-**6**	 **24**	49	–
15	 (*Z*)-**6**	**24**	56	–

[a] Yields do not reflect recovered starting ketone and are based upon products isolated from preparative TLC. [b] Estimated by using relative areas of the HPLC peaks obtained by monitoring at the absorption maximum for the crude mixture. [c] Literature[25] yield 84%.

21 gave only the 1,4-addition products **25** and **26**, even though the conditions employed typically result in 1,2-addition to enones.[13] It should also be noted that the most sterically crowded vinylogous bromo ester **6** reacted with 2-methylcyclohexanone (**15**) to produce lactone **24**, while enone **5** yielded the unprecedented carboxylic acid **8**. The stereochemistry of **8** and the δ-lactone product resulting from the reaction of **15** and **6** strongly support the formation of **8** via a δ-lactone intermediate. These observations imply that carbonyl substrates that are highly unreactive toward 1,2-addition of vinylogous Reformatsky reagents (due to steric and/or electronic effects) require δ-lactone formation for successful reactions.

These studies also revealed that the starting configuration of the vinylogous bromo ester had no effect on the composition of the reaction products. As shown in Tables II and III, the reactions of pure (*E*) or (*Z*)-bromo esters with **15** and **5** gave the same product mixtures. Of particular interest is the observation that vinylogous Reformatsky reagents resulting from bromo esters **6** and **21** both gave stereomutated products, and it can be concluded that intermolecular allylic hydrogen transfer is not required for *E*–*Z* isomerization.

The Reformatsky reaction was recently demonstrated to be reversible.[13] The results described here are consistent with a reversible addition of the zinc dienolate, which is capable of undergoing s-trans, s-cis isomerization, to the ketone carbonyl. For very unfavorable additions (due to steric and electronic effects), γ-attack by the *s-cis*-dienolate results in an alkoxide intermediate which can readily form lactone, driving the unfavorable equilibrium toward product. It follows that lactone formation may be required for successful Reformatsky reactions of this type under very unfavorable conditions, such as the reactions of **6** with **5** and **15**.

Current efforts are focused on the isomerization of **8** to the *all-E* configuration and further elaboration to form **2**.

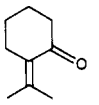
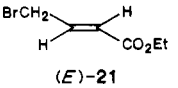
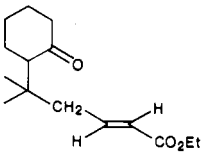
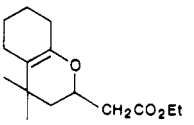
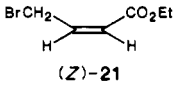
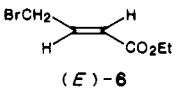
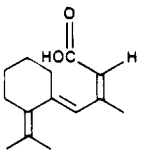
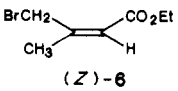
Experimental Section

Ethyl (diethoxyphosphinyl)ethanoate (**10**), ethyl 4-(diethoxyphosphinyl)-3-methylbut-2-enoate (**4**), and ethyl 4-(diethoxyphosphinyl)but-2-enoate (**12**) were prepared via the Arbusov reaction.[21] 2-Isopropylidenecyclohexanone (**5**) was prepared as previously described.[22] An *E,Z* mixture of ethyl 4-bromo-3-methylbut-2-enoate (**6**) was prepared by the reaction of ethyl 3,3-dimethylacrylate with *N*-bromosuccinimide,[14,23,24] and the isomers were separated by preparative HPLC (Whatman Partisil 10 M20/50 (500 mm l × 22 mm i.d., 8 mL/min, 2% ether/hexane, 220 nm): retention times (*Z*) 31.4 min (38%) and (*E*) 41.4 min. (51%). Ethyl 2-(1-hydroxy-2-methylcyclohexyl)ethanoate (**20**) was prepared according to the procedure by Matsumoto and Fukui.[25] A published procedure[26] was used to prepare an *E,Z* mixture of ethyl 2-cyclohexylideneacetate (**11**). An *E,Z* mixture of ethyl 2-methylcyclohexylideneacetate (**16**) was prepared as previously described,[27] and the isomers were separated by preparative HPLC (Whatman Partisil 10 M9/50, 3 mL/min, 2% ether/hexane, 230 nm): retention times (*Z*) 18.0 min (22.6%) and (*E*) 19.5 min (77.4%).

UV/vis spectra were obtained on a Beckman Model 26 spectrophotometer, and IR spectra were obtained on a Beckman Acculab 6 spectrometer. NMR spectra were obtained on a GE wide-bore spectrometer (NT series) equipped with an 1180e computer and 293c pulse programmer. The resonance frequency

(21) Arbusov, A. E. *Pure Appl. Chem.* **1964**, *9*, 307.
(22) Corey, E. J.; Chen, R. H. K. *Tetrahedron Lett.* **1973**, *39*, 3817.
(23) Ahmad, I. L.; Gegye, R. N.; Nechvatal, A. *J. Chem. Soc. C* **1968**, 185.
(24) Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984.
(25) Matsumoto, T.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1971**, *4*, 1090.
(26) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(27) Musierowicz, S.; Wroblewski, A.; Krawezyk, H. *Tetrahedron Lett.* **1975**, *7*, 437.

Table III. Reformatsky Reactions of Enone 5

enone	bromo ester	product	isolated % yield[a]	product composition,[b] %
 5	$BrCH_2CO_2Et$ 19	no reaction	–	–
5	 (*E*)-21	 25 +  26	42 (mixture)	50 50
5	 (*Z*)-21	25 + 26	49 (mixture)	37 63
5	 (*E*)-6	 8	15	–
5	 (*Z*)-6	8	28	–

[a,b] See Table II.

for ^1H was 300.1 MHz and for ^{13}C was 75.5 MHz. All spectra were obtained in $CDCl_3$ at ambient temperature. Proton spectra were internally referenced to tetramethylsilane (TMS), and carbon spectra were internally referenced to $CDCl_3$ (77.0 ppm from TMS). In the homonuclear NOE experiments the solution of 8 was bubbled with N_2 gas for 30 min and the NMR tube was sealed with parafilm. The delay time (10 s) and decoupling power (43 db) were varied to obtain maximum NOE. Two experiments were run with the decoupler frequency set on-resonance and off-resonance (2500 Hz), and the spectra were digitally subtracted to give a difference spectrum. The fraction of NOE was calculated by the ratio of the integrated areas of the peaks in the difference spectrum to that of the off-resonance spectrum.

GC/MS spectra were obtained on a Hewlett-Packard 5985 spectrometer. HPLC separations were accomplished with use of a Whatman Partisil 10 M9/50 or M20/50 column on a Rainin Rabbit HPLC system, which included an Apple IIe controlled Gilson Data Master and a Hitachi Model 100-40 variable-wavelength detector. All solvents were HPLC grade (Fischer Omni-Solve) and were saturated with dry nitrogen and degassed by vacuum filtration through a Millipore filter (0.45 μm) prior to use. Elemental analyses were obtained from Atlantic Microlab of Atlanta, GA.

General Method for Horner–Emmons Reactions. (Additional quantities and concentrations are given below for each compound.) NaH (50% oil dispersion) was washed free of mineral oil with three successive washings of THF. This was resuspended in THF with stirring and chilled in an ice bath. The appropriate phosphonate ester was then added dropwise via syringe. The reaction was gradually allowed to warm to room temperature over 90 min. The ylide solution was rechilled to 0 °C, and 1–2 mL of hexamethylphosphoramide was added followed by the dropwise addition (via syringe) of the appropriate ketone or enone. The reactions were allowed to proceed (4–48 h) until TLC (silica gel, 10% acetone/hexane) indicated no further change. The reaction mixture was extracted with water (10 mL), and the aqueous layer was further extracted with ether (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo at less than 30 °C. Products were purified utilizing preparative TLC (silica gel, Analtech GF, 20 × 20 × 0.2 cm, 10% acetone/hexane). Starting ketone was present at the conclusion of the reaction in each case as evidenced by TLC but was not recovered by preparative chromatography. The reported isolated yields do not account for the amount of unreacted ketone. By this procedure were prepared compounds **13**, **14**, **17**, and **18** as follows.

Ethyl 4-Cyclohexylidenebut-2-enoate (13). The reaction of phosphonate ester **12** (500 mg, 2.0 mmol) and NaH (93 mg, 1.9 mmol) in 15 mL of THF followed by the addition of cyclohexanone (**9**, 167 mg, 1.70 mmol) gave **13** (110 mg, 32%). The ^1H NMR, IR, and mass spectra were identical with those reported[28] for **13** prepared by another method.

Ethyl 3-Methyl-4-cyclohexylidenebut-2-enoate (14). The reaction of **4** (1.44 g, 5.46 mmol) with NaH (260 mg, 5.42 mmol) followed by the addition of **9** (555 mg, 5.64 mmol) in 30 mL of THF gave **14** (319 mg, 28.2%). GC/MS indicated a mixture of two isomers (relative abundance 3:17), which were not separated: R_f 0.84; ^1H NMR δ 5.66 (s, 1 H, vinyl), 5.63 (s, 1 H, vinyl), 4.14 (q, 2 H, OCH_2), 2.34 (m, 2 H, allylic CH_2), 2.22 (s, 3 H, allylic CH_3), 2.15 (m, 2 H, allylic CH_2), 1.57 (m, 6 H, cyclohexyl CH_2), 1.27 (t, 3 H, OCH_2CH_3); UV(MeOH, λ_{max}) 270, 206 nm; IR (neat) 1710 (C=O), 1630 (C=C) cm^{-1}; MS (70 eV) *m/e* 208 (M^+). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.88; H, 9.68.

Ethyl 4-(2-Methylcyclohexylidene)but-2-enoate (17). The reaction of **12** (548 mg, 2.19 mmol) with NaH (105 mg, 2.18 mmol) followed by the addition of 2-methylcyclohexanone (**15**, 235 mg, 2.09 mmol) in 15 mL of THF gave **17** (91 mg, 21%). GC/MS

(28) Huang, Y.; Shen, Y.; Zheng, J.; Zhang, S. *Synthesis* **1985**, 57.

indicated a mixture of two isomers (relative abundance 2:23), which were not separated: R_f 0.84; ^{1}H NMR δ 7.67 (d of d, 1 H, C-3 vinyl), 5.93 (d, 1 H, C-4 vinyl), 5.83 (d, 1 H, C-2 vinyl), 4.19 (q, 2 H, OCH_2), 2.80 (m, 1 H, $CHCH_3$), 2.5–1.4 (m, 8 H, cyclohexyl CH_2), 1.29 (t, 3 H, OCH_2CH_3), 1.05 (m, 3 H, $CHCH_3$); UV (MeOH, λ_{max}) 265, 219 nm; IR (neat) 1700 (C=O), 1640 (C=C) cm^{-1}; MS (70 eV) m/e 208 (M^+). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.93; H, 9.72.

Ethyl 4-(2-Methylcyclohexylidene)-3-methylbut-2-enoate (18). The reaction of **4** (2.36 g, 8.92 mmol) with NaH (427 mg, 8.90 mmol) followed by the addition of **15** (1.00 g, 8.95 mmol) in 50 mL of THF gave **18** (198 mg, 10.0%). GC/MS indicated a mixture of three isomers (relative abundance 4:6:11), which were not separated: R_f 0.81; ^{1}H NMR δ 5.62 (s, 2 H, vinyl), 4.17 (q, 2 H, OCH_2), 2.70 (m, 1 H, $CHCH_3$), 2.22 (s, 3 H, C-3 CH_3), 2.20–1.32 (m, 8 H, cyclohexyl CH_2), 1.28 (t, 3 H, OCH_2CH_3), 1.05 (d, 3 H, $CHCH_3$); UV (MeOH, λ_{max}) 305 nm; IR (neat) 1700 (C=O) cm^{-1}; MS (70 eV) m/e 222 (M^+). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.55; H, 10.05.

General Method for Reformatsky Reactions. (Additional quantities and concentrations are described below for each compound.) Zinc dust was activated according to the procedure of Hauser.[29] The activated zinc was resuspended in 1–2 mL of benzene and brought to reflux. To the refluxing solution was added via syringe approximately 0.2 mL of a solution containing 1 mL of benzene, ketone, and bromo ester. Vigorous bubbling accompanied by the appearance of a green color was normally observed within 20 min (a crystal of iodine was occasionally added to begin the reaction). Once the reaction had begun the remaining benzene solution of ketone and bromo ester was added dropwise via syringe. The reaction was allowed to proceed at reflux until TLC (silica gel, 20% ether/hexane) indicated no further change (2–24 h). TLC revealed that starting ketone, which was not recovered and thus not accounted for in yield calculations, was present at the conclusion of each reaction. The reaction mixture was cooled to room temperature, 1 mL of water was added, the solution was stirred for 30 min, and the supernatant was withdrawn. In a similar manner the aqueous zinc suspension was washed with additional ether (3 × 5 mL). The combined organic extracts were concentrated in vacuo, and the residue was separated by preparative TLC (silica gel, Analtech GF, 20 × 20 × 0.2 cm, 10% acetone/hexane). By this method were prepared compounds **8** and **22–26** as follows.

(2*Z*,4*E*)-3-Methyl-4-(2-isopropylidenecyclohexylidene)-but-2-enoic Acid (8). The reaction of **5** (495 mg, 3.59 mmol) and either pure (*E*)- or pure (*Z*)-**6** (769 mg, 3.73 mmol) with Zn dust (887 mg, 13.6 mmol) gave **8** [118 mg, 15.0% from (*E*)-**6**; 219 mg, 27.8% from (*Z*)-**6**]. GC/MS indicated that each product contained only one isomer: R_f 0.25; ^{1}H NMR δ 6.01 (s, 1 H, C-4 vinyl), 5.72 (s, 1 H, C-2 vinyl), 2.26 (t, 2 H, C-13 CH_2), 2.17 (t, 2 H, C-10 CH_2), 2.02 (s, 3 H, C-3 CH_3), 1.79 (s, 3 H, C-9 CH_3), 1.69 (s, 3 H, C-8 CH_3), 1.58 (m, 4 H, ring CH_2); ^{13}C NMR ($CDCl_3$) δ 171.65 (C=O), 155.87 (C-7), 145.51 (C-5), 135.51 (C-3), 124.22 (C-6), 123.87 (C-4), 117.13 (C-2), 31.96 (C-13), 31.69 (C-10), 27.75 (CH_2), 27.25 (CH_2), 26.13 (CH_3), 21.87 (CH_3), 20.06 (C-3 CH_3); UV (MeOH, λ_{max}) 211, 265 nm; IR (neat) 3200 (broad, —OH), 1680 (C=O), 1600 (C=C) cm^{-1}; MS (70 eV) m/e 220 (M^+). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.25; H, 9.15.

(*E*)-Ethyl 4-(1-Hydroxy-2-methylcyclohexyl)but-2-enoate (22) and 7-Methyl-1-oxaspiro[5.5]undec-3-en-2-one (23). The reactions of **15** (250 mg, 2.23 mmol) with either pure (*E*)- or pure (*Z*)-**21** (400 mg, 2.08 mmol) and zinc dust (545 mg, 8.34 mmol) each gave product mixtures containing **22** and **23**, which eluted on TLC as a single spot (R_f 0.30). GC/MS indicated that each product consisted of two isomers. HPLC separation (M9/50, 3 mL/min, 230 nm, 10% ether/10% THF/hexane) of the mixture yielded the following.

Compound **22** was isolated as two diastereomers with retention times 20.43 min (**22a**) and 23.94 min (**22b**); relative abundance (**a**:**b**) for the reaction with (*E*)-**21** was 3:7 and that for (*Z*)-**21** was 2:3. Relative stereochemistry was not determined. The yield of the combined diastereomers from the reaction with (*E*)-**21** was 98 mg (25%) and that from the reaction with (*Z*)-**21** was 42 mg (8.9%). For the combined diastereomers: IR (neat) 3460 (broad, —OH), 1690 (C=O) cm^{-1}; MS (70 ev) m/e 208 (M^+ – 18). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.05; H, 9.82. For **22a**: ^{1}H NMR δ 6.97 (d of t, 1 H, J = 15.6 Hz, C-3 vinyl), 5.87 (d, 1 H, J = 15.6 Hz, C-2 vinyl), 4.21 (q, 2 H, OCH_2), 2.39 (d of d, 2 H, allylic CH_2), 1.74–1.0 (m, 12 H, ring CH_2, $CHCH_3$, and OCH_2CH_3), 0.91 (d, 3 H, $CHCH_3$); UV (MeOH, λ_{max}) 222 nm. For **22b**: ^{1}H NMR δ 7.07 (d of d, 1 H, J = 15.6 Hz, C-3 vinyl), 5.89 (d, 1 H, J = 15.6 Hz, C-2 vinyl), 4.18 (q, 2 H, OCH_2), 2.34 (d of t, 2 H, allylic CH_2), 1.8–1.0 (m, 12 H, ring CH_2, $CHCH_3$, and OCH_2CH_3), 0.95 (d, 3 H, CH_3); UV (MeOH, λ_{max}) 218 nm.

Lactone **23** was also obtained as two diastereomers with HPLC retention times of 26.16 min (**23a**) and 27.66 min (**23b**); relative abundance (**a**:**b**) for the reaction with (*E*)-**21** was 4:1 and that for (*Z*)-**21** was 4:1. Relative stereochemistry was again not determined. The yield of the combined diastereomers from the reaction with (*E*)-**21** was 58 mg (15%) and that for (*Z*)-**21** was 12 mg (3.1%, 23b). For the combined diastereomers: IR (neat) 1680 (C=O) cm^{-1}; MS (70 eV) m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.09; H, 9.01. For **23a**: ^{1}H NMR δ 6.56 (m, 1 H, C-4 vinyl), 5.99 (d, 1 H, J = 9.6 Hz, C-3 vinyl), 2.79 (m, 1 H, C-5 CH_2), 2.30 (m, 1 H, C-5 CH_2), 2.10 (d, 1 H, $CHCH_3$), 1.8–1.0 (m, 8 H, CH_2), 1.00 (d, 3 H, CH_3); UV (MeOH, λ_{max}) 217 nm. For **23b**: ^{1}H NMR δ 6.75 (m, 1 H, C-4 vinyl), 6.01 (d, 1 H, J = 9.6 Hz, C-3 vinyl), 2.51 (d, 1 H, C-5 CH_2), 2.34 (d, 1 H, C-5 CH_2), 2.1–1.0 (m, 9 H, CH_2 and $CHCH_3$), 0.98 (d, 3 H, CH_3); UV (MeOH, λ_{max}) 225 nm.

4,7-Dimethyl-1-oxaspiro[5.5]undec-3-en-2-one (24). The reaction of **15** (903 mg, 8.05 mmol) and either pure (*E*)- or pure (*Z*)-**6** (1.82 g, 8.75 mmol) with Zn dust (1.60 g, 24.4 mmol) gave **24** [760 mg, 49% from (*E*)-**6** and 868 mg, 56% from (*Z*)-**6**]: R_f 0.30; ^{1}H NMR δ 5.76 (b s, 1 H, C-3 vinyl), 2.75 (d, 1 H, C-5 CH_2), 2.22 (d, 1 H, C-5 CH_2), 2.00–1.96 (m, 4 H, $CHCH_3$ and C-4 CH_3), 1.72–1.19 (m, 8 H, ring CH_2), 0.98 (d, 3 H, $CHCH_3$); UV (MeOH, λ_{max}) 227 nm; IR (neat) 1680 (C=O) cm^{-1}; MS (70 eV) m/e 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.06; H, 9.39.

Ethyl 5,5-Dimethyl-5-(2-oxocyclohexyl)pent-2-enoate (25) and 2-[(Ethoxycarbonyl)methyl]-3,4,5,6,7,8-hexahydro-4,4-dimethyl-2*H*-1-benzopyran (26). The reactions of **5** (110 mg, 0.82 mmol) with pure (*E*)- or pure (*Z*)-**21** (170 mg, 0.89 mmol) and Zn dust (197 mg, 3.01 mmol) each gave product mixtures containing the same two components, **25** and **26**.

The yield of compound **25** was 43 mg (21%) for the reaction with (*E*)-**21** and that for (*Z*)-**21** was 37 mg (18%): R_f 0.40; ^{1}H NMR δ 6.95 (d of t, 1 H, C-3 vinyl), 5.80 (d, 1 H, J = 15.6 Hz, C-2 vinyl), 4.19 (q, 2 H, OCH_2), 2.60–1.40 (m, 11 H, CH_2, CH, and allylic CH_2), 1.29 (t, 3 H, OCH_2CH_3), 1.06 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.41 (ketone C=O), 166.55 (ester C=O), 146.36 (C-3), 123.53 (C-2), 60.17 (OCH_2), 58.04 (C-6), 44.19 (C-4), 42.90 (CH_2C=O), 35.45 (C-5), 29.51 (CH_2), 28.61 (CH_2), 26.01 (CH_2), 25.63 (C-5 CH_3), 24.35 (C-5 CH_3), 14.26 (OCH_2CH_3); UV (MeOH, λ_{max}) 350, 219 nm; IR (neat) 1720 (C=O, ester), 1655 (C=O, ketone) cm^{-1}; MS (70 eV) m/e 252 (M^+). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 70.98; H, 9.68.

The yield of compound **26** was 43 mg (21%) for the reaction with (*E*)-**21** and that for (*Z*)-**21** was 64 mg (31%): R_f 0.50; ^{1}H NMR δ 4.30–4.10 (m, 2 H, OCH_2), 2.54 (m, 1 H, OCH), 1.97 (b s, 4 H, allylic CH_2), 1.75–1.32 (m, 8 H, CH_2), 1.28 (t, 3 H, OCH_2CH_3), 1.07 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.14 (C=O), 144.95 (C-4a), 111.72 (C-8a), 68.32 (OCH_2), 60.44 (C-2), 44.52 (CH_2C=O), 41.07 (C-3), 31.20 (CH_2), 28.12 (CH_3), 27.86 (CH_3), 27.49 (CH_2), 23.27 (CH_2), 23.08 (CH_2), 22.70 (CH_2), 14.24 (OCH_2CH_3); UV (MeOH, λ_{max}) 215 nm; IR (neat) 1700 (C=O) cm^{-1}; MS (70 eV) m/e 252 (M^+). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.56.

(*Z*)-Ethyl 4-Bromobut-2-enoate (21). In a pressure bottle was reacted (carbethoxymethylene)triphenylphosphorane (5.66 g, 16.3 mmol) and bromoacetaldehyde (2.74 g, 22.4 mmol) in 50 mL of ethanol at 45 °C for 3 h. The reaction was cooled to room temperature, and the ethanol was removed under vacuum. Water (10 mL) was added, the solution was extracted with 3 × 50 mL of ether, and the combined ether layers were dried (Na_2SO_4) and concentrated in vacuo to give an *E*,*Z* mixture of crude **21**. Preparative TLC on silica (1% MeOH/10% acetone/hexane) yielded (*E*)-**21** (R_f 0.45, 1.9 g, 60%) and (*Z*)-**21** (R_f 0.60, 600 mg,

(29) Hauser, C. R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 408.

19%) as colorless oils. For (*Z*)-**21**: ^{1}H NMR δ 6.40 (m, 1 H, C-3 vinyl), 5.81 (d, 1 H, *J* = 11.07 Hz, C-2 vinyl), 4.54 (d, 2 H, allylic), 4.20 (q, 2 H, OCH_2), 1.31 (t, 3 H, OCH_2CH_3); UV (MeOH, λ_{max}) 226 nm; IR (neat) 1705 (C=O), 1625 (C=C) cm^{-1}; MS (70 eV) *m/e* 190 (M^+), 192 ($M^+ + 2$). Anal. Calcd for $C_6H_9O_2Br$: C, 37.33; H, 4.70. Found: C, 37.46; H, 4.75.

Acknowledgment. We thank D. Vincent Waterhous for conducting the NOE studies. This work was supported in part by Research Grants CA13148 and P01CA28103-08 from the National Cancer Institute.

Registry No. **2**, 119011-78-8; **3**, 119011-79-9; **4**, 39760-56-0; **5**, 13747-73-4; (*E*)-**6**, 51318-62-8; (*Z*)-**6**, 51371-55-2; **8**, 119011-80-2; **9**, 108-94-1; **10**, 867-13-0; **11**, 1552-92-7; **12**, 42516-28-9; **13**, 97856-56-9; **14**, 119011-81-3; (*Z*)-**14**, 119011-77-7; **15**, 583-60-8; **16**, 2209-00-9; (*Z*)-**16**, 2208-99-3; **17**, 119011-82-4; **18**, 119011-83-5; **19**, 105-36-2; **20**, 5108-87-2; (*E*)-**21**, 37746-78-4; (*Z*)-**21**, 119011-89-1; *cis*-**22**, 119011-84-6; *trans*-**22**, 119068-56-3; *cis*-**23**, 119011-85-7; *trans*-**23**, 119011-90-4; **24**, 119011-86-8; **25**, 119011-87-9; **26**, 119011-88-0; $(CH_3)_2C{=}CHCO_2Et$, 638-10-8.

Formation of Cis-Fused Cyclopentanoids by Michael Addition and Radical Cyclization

Derrick L. J. Clive* and Taryn L. B. Boivin

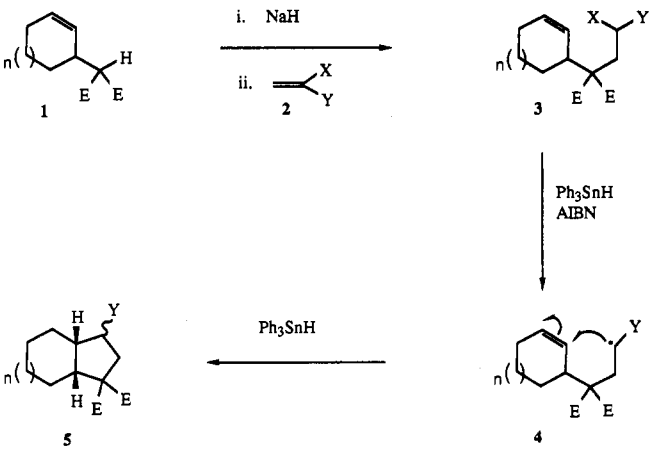
Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Received September 6, 1988

Many natural products contain cyclopentane substructures,[1] and so the development of methods for preparing five-membered carbocycles has received much attention.[2] Synthetic access to these materials using modern free radical methods[3] depends, of course, on the availability of general and straightforward ways of making the required radical precursors, and a number of studies have been published in this area.[4] We have found that the Michael reaction, when used in the manner summarized by Scheme I, and followed by radical cyclization (**3** → **4** → **5**), provides a convenient route to cis-fused cyclopentanoids. A characteristic of this strategy (Scheme I) is that the starting materials are easily prepared, not only by classical nucleophilic displacement with malonate anion, but, more importantly, by a general ene process,[5] which proceeds in suitable cases (Scheme II) with predictable stereo- and regiochemistry.

We examined a number of Michael acceptors and, of those that we tested (**2a–d**), the sulfones **2a,b** and the ester **2c** are the most useful as both reactions **1** → **3** and **3** → **5** of Scheme I generally proceed in satisfactory yield (see Table I).[6] With the exception of example **1f**, in which

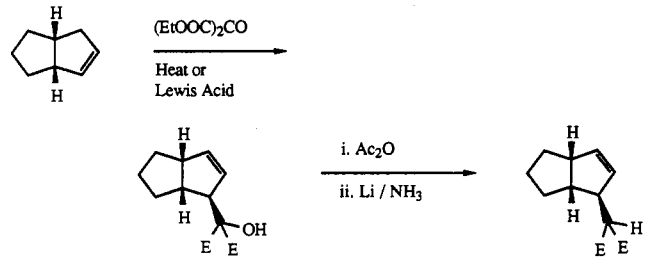
Scheme I[a]



2a: X = Br, Y = SO_2Ph; 2b: X = Br, Y = SO_2Bu^t
2c: X = SePh, Y = COOMe; 2d: X = Br, Y = COOMe

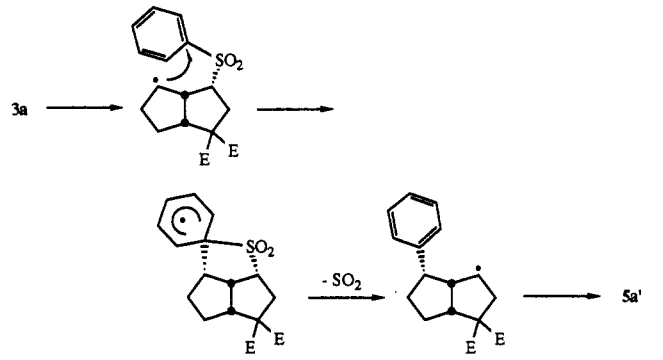
[a] E = COOEt.

Scheme II[a]



[a] E = COOEt.

Scheme III[a]



[a] E = COOEt.

---

(1) See, e.g.: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1 and references therein.

(2) Review: Ramaiah, M. *Synthesis* **1984**, 529.

(3) Curran, D. P. *Synthesis* **1988**, 417 and 489. Hart D. J. *Science* **1984**, *223*, 883. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(4) (a) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (b) Barton, D. H. R.; da Silva, E.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 285. (c) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893. (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377. (e) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313. (f) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 980. (g) Set, L.; Cheshire, D. R.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1205. (h) Mohammed, A. Y.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 588. (i) Clive, D. L. J.; Cheshire, D. R.; Set, L. *J. Chem. Soc., Chem. Commun.* **1987**, 353. (j) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520. (k) Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943. (l) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (m) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210. (n) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218. (o) Leonard, W. R.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 6431. (p) Pattenden, G.; Robertson, G. M. *Tetrahedron* **1985**, *41*, 4001. (q) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (r) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (s) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3721. (t) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. (u) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 546. (v) Zeigler, F. E.; Zhong-li, Zheng *Tetrahedron Lett.* **1987**, *28*, 5973. (w) Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897.

(5) (a) Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1984**, *49*, 2446. (b) Salomon, M. F.; Pardo, S. N.; Salomon, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 3797. (c) Pardo, S. N.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1981**, *22*, 1885. In the deoxygenation step of Scheme II of this reference, Li/NH_3 should be used; in out hands the procedure reported in Table I of ref 5c did not work.

0022-3263/89/1954-1997$01.50/0