N^6-Butyladenosine (VIIb) was prepared in analogy to VIIa from chloro nucleoside I (0.2 g, 0.70 mmol), 1-aminobutane (0.14 ml, 1.4 mmol), and triethylamine (0.29 ml, 2.1 mmol) in DMF (1.5 ml). After evaporation, the residue was crystallized from methanol to give 0.16 g (71%) of VIIb: mp 171–173 °C (lit.[21] 176 °C); $[\alpha]^{25}D$ −36.4° (*c* 0.5, CH_3SOCH_3); UV max (H_2O) 268 nm (ε 17 600); (0.01 N HCl) 264 nm (ε 17 900); NMR (CD_3SOCD_3) δ 8.22 (s, 1, H_8), 8.10 (s, 1, H_2), 5.83 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6 Hz), 7.63 (poorly resolved t, disappeared on addition of D_2O, NH), ca. 5.2 (poorly resolved m, disappeared on addition of D_2O, OH), the rest of the ribose proton signals and NCH_2 at δ 3.3–4.5 are not well resolved, ca. 1.47 and 0.88 (poorly resolved m, 7, CCH_2 and CH_3). Anal. Calcd for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.56; N, 21.66. Found: C, 51.88; H, 6.60; N, 21.82.

Acknowledgments. The authors are indebted to Dr. P. A. Scherr for computer calculations and to Dr. E. B. Hills for measurement of the NMR spectra. Biological tests in murine leukemia L1210 in vitro system were performed by Dr. D. Kessel.

Registry No.—I, 23828-03-7; IIa, 107-15-3; IIb, 110-60-1; IIIb, 60687-64-1; IIIc, 60687-65-2; IVa, 35662-04-5; IVb, 60687-66-3; V, 39824-26-5; VI, 60687-67-4; VIIa, 14357-08-5; VIIb, 23096-10-8; ethylamine HCl, 557-66-4; butylamine, 109-73-9.

References and Notes

(1) (a) This investigation was supported in part by U.S. Public Health Service Research Grants GM-19108 and GM-21093 from the National Institute of General Medical Sciences and in part by an institutional grant to the Michigan Cancer Foundation from the United Foundation of Greater Detroit. (b) Presented in part at the 9th International Symposium on Chemistry of Natural Products, Ottawa, Canada, June 1974, Abstract, p 31B.
(2) For a review of protein biosynthesis, see P. Lengyel and D. Söll, *Bacteriol. Rev.*, **33**, 264 (1969).
(3) The possibility of stacking of both peptidyl and aminoacyl tRNA "donor–acceptor stacking" was recognized earlier: (a) I. D. Raacke, *Biochem. Biophys. Res. Commun.*, **43**, 168 (1971); (b) J. Zemlicka, S. Chládek, D. Ringer, and K. Quiggle, *Biochemistry*, **14**, 5239 (1975).
(4) (a) F. Seela and F. Cramer, *Chem. Ber.*, **108**, 1329 (1975); (b) F. Seela and V. A. Erdmann, *Biochim. Biophys. Acta*, **435**, 105 (1976).
(5) M. Ya. Feldman, E. S. Zalmanson, and L. N. Mikhailova, *Mol. Biol. (Moscow)*, **5**, 847 (1971).
(6) (a) H. Lettré and H. Ballweg, *Naturwissenschaften*, **45**, 364 (1958); (b) *Justus Liebigs Ann. Chem.*, **649**, 124 (1961).
(7) T. Alderson, *Nature (London) New Biol.*, **244**, 3 (1973).
(8) J. H. Lister, *J. Chem. Soc.*, 3394 (1960).
(9) N. J. Leonard and K. Ito, *J. Am. Chem. Soc.*, **95**, 4010 (1973).
(10) (a) M. Ya. Feldman, *Biokhimiya*, **27**, 378 (1962); (b) *Prog. Nucleic Acid Res. Mol. Biol.*, **13**, 11 (1973).
(11) H. Lettré and H. Ballweg, *Justus Liebigs Ann. Chem.*, **656**, 158 (1962).
(12) D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Am. Chem. Soc.*, **90**, 7302 (1968).
(13) C. R. Cantor, M. M. Warshaw, and H. Shapiro, *Biopolymers*, **9**, 1059 (1970), and references cited therein.
(14) J. Zemlicka and F. Sorm, *Collect. Czech. Chem. Commun.*, **30**, 1880 (1965).
(15) P. S. Miller, K. N. Fang, N. S. Kondo, and P. O. P. Ts'o, *J. Am. Chem. Soc.*, **93**, 6657 (1971).
(16) CD measurements in 5×10^{-2} M Tris buffer (pH 7.4) gave essentially identical results with those in water (pH 7.0). No influence of 1×10^{-2} M $MgCl_2$ on the CD curve of IIIb and IIIc has been found in the above buffer.
(17) Two conformers of IIIb and IIIc with respect to the mutual orientation of bases in a stacked structure are possible[18] (Figure 4) if we neglect the differences in rotameric composition owing to the presence of an aliphatic chain, ribose residues (syn–anti conformers), and situations not involving a total overlap of bases.
(18) C. E. Bugg, U. T. Thewalt, and R. E. Marsh, *Biochem. Biophys. Res. Commun.*, **33**, 436 (1968), Figure 2.
(19) M. M. Warshaw and I. Tinoco, Jr., *J. Mol. Biol.*, **20**, 29 (1966).
(20) N. S. Kondo, H. M. Holmes, L. M. Stempel, and P. O. P. Ts'o, *Biochemistry*, **9**, 3479 (1970).
(21) M. H. Fleysher, *J. Med. Chem.*, **15**, 187 (1972).
(22) J. J. McCormick, V. M. Maher, and J. Zemlicka, *Biochem. Pharmacol.*, submitted.
(23) J. Zemlicka, R. Gasser, J. V. Freisler, and J. P. Horwitz, *J. Am. Chem. Soc.*, **94**, 3213 (1972).
(24) Compounds IIIb and IIIc are not well soluble in water or in 0.01 N HCl. Moreover, it has been found that IIIb is less stable toward acids (HCl) than ordinary purine ribonucleosides. It is, therefore, imperative not to prepare stock solutions of IIIb and IIIc in 0.01 N HCl.
(25) A. Hampton and M. H. Maguire, *J. Am. Chem. Soc.*, **83**, 150 (1961).
(26) S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).
(27) These values differ from those reported in the literature[11] (ϵ_{max} 28 300 and 28 800, respectively, for pH 7 and 1). The Beer's law was followed for both IIIb and IIIc at pH 7 within the absorbancy range 0.25–1.4.
(28) In one case where the triethylamine hydrochloride was not removed, the crude mixture was directly put on the Dowex 50 column, and the chromatography was run at room temperature, a partial cleavage of the nucleoside bond in IIIc was observed as detected by electrophoresis in borate buffer. This was apparently due to the presence of an excess HCl released from the triethylamine hydrochloride by the action of Dowex 50 (H^+ form).

Protection of Aspartic Acid, Serine, and Threonine in Solid-Phase Peptide Synthesis

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Received August 11, 1976

N-Boc-β-(4-bromobenzyl)aspartic acid, *N*-Boc-*O*-(4-bromobenzyl)serine, and *N*-Boc-*O*-(4-chlorobenzyl)threonine have been synthesized for use in solid-phase peptide synthesis. The side-chain protecting groups were five to seven times more stable than the parent benzyl protection in 50% trifluoroacetic acid in dichloromethane and were completely removed in liquid hydrogen fluoride at 0 °C in 10 min.

Included among recent improvements in solid-phase peptide synthesis[1] is the development of side-chain protecting groups based on quantitative measurements of their stabilities.[2,3] Since *N*-Boc protection[4,5] is commonly employed along with final deblocking in liquid hydrogen fluoride,[6] the ideal protecting group is completely stable during removal of the Boc group and completely removed in HF. We now report the synthesis and properties of three new derivatives directed toward this end.

The removal of the Boc group is effectively accomplished in 50% trifluoroacetic acid in dichloromethane.[7] Benzyl protection of the side chains of serine, threonine, and aspartic acid has been shown to be sufficiently stable in this reagent for synthesis of peptides of moderate size.[2,3] However, it would be desirable to have protecting groups for these amino acids of even greater stability. Therefore, *N*-Boc-β-(4-bromobenzyl)aspartic acid (I), *N*-Boc-*O*-(4-bromobenzyl)serine (II), and *N*-Boc-*O*-(4-chlorobenzyl)threonine (III) were synthesized with II and III isolated as dicyclohexylamine salts. All three compounds were prepared by procedures analogous to those developed for the corresponding benzyl derivatives. The steric purity of the new derivatives was assessed by two criteria.

For testing the behavior of the new protecting groups, compounds I, II, and III were converted to *N*-acetylamide derivatives (Ia, IIa, and IIIa in Table I), where any influence

Table I. Stabilities of Side-Chain Protecting Groups in Trifluoroacetic Acid

Compd tested[a]	Time of treatment, h[f]	Loss of protection, %
Benzyl N^{α}-acetylisoasparaginate (benzyl 3-acetaminosuccinamate)[b]	23	4
4-Bromobenzyl N^{α}-acetylisoasparaginate (4-bromobenzyl 3-acetaminosuccinamate, Ia)[c]	71	2.5
N^{α}-Acetyl-*O*-benzylserineamide[b]	23	3
N^{α}-Acetyl-*O*-(4-bromobenzyl)serineamide[d] (IIa)	71	1.3
N^{α}-Acetyl-*O*-benzylthreonineamide[b]	23	5
N^{α}-Acetyl-*O*-(4-chlorobenzyl)-threonineamide[e] (IIIa)	71	2.5

[a] Prepared by conversion of the Boc-amino acid to the amide by the mixed anhydride method followed by treatment with TFA and acetylation with acetic anhydride in pyridine. [b] Data from ref 2. [c] Mp 145–146.5 °C. Anal. Calcd for $C_{13}H_{15}BrN_2O_4$ (343.18): C, 45.50; H, 4.41; N, 8.16. Found: C, 45.57; H, 4.43; N, 8.13. [d] Mp 151–152 °C. Anal. Calcd for $C_{12}H_{15}BrN_2O_3$ (315.17): C, 45.73; H, 4.80; N, 8.89. Found: C, 45.86; H, 4.82; N, 8.89. [e] Mp 187.5–190 °C. Anal. Calcd for $C_{13}H_{17}ClN_2O_3$ (284.74); C, 54.84; H, 6.02; N, 9.84. Found: C, 54.92; H, 6.01; N, 9.99. [f] In 50% TFA in CH_2Cl_2 at 24 °C.

of the amino and α-carboxyl groups is removed. Each was treated with 50% trifluoroacetic acid in dichloromethane and the loss of side-chain protection estimated by thin layer chromatography as shown in Table I. All three protecting groups were about five to seven times more stable than the corresponding benzyl protection. Even more stable protecting groups are possible but the use of these must be weighed against ease of removal in HF since excessive exposure to this reagent is not recommended.[8] All three protecting groups were removed completely (>99%) by treatment with HF for 10 min at 0 °C.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Thin layer chromatography (TLC) was run on silica gel in the following solvents: chloroform–acetic acid, 15:1 (CA); 1-butanol–acetic acid–water, 4:1:1 (BAW).

β-4-Bromobenzyl Aspartate. This compound was prepared by the general method of Ledger and Stewart[9] with the exception that the volume of water used in preparing lithium copper(II) aspartate was reduced fourfold to eliminate a time-consuming evaporation step: overall yield 26%; mp 220–223 °C; TLC (BAW) R_f 0.55; $[\alpha]^{24}D$ +14.1° (*c* 2, 80% acetic acid).

Anal. Calcd for $C_{11}H_{12}BrNO_4$ (302.13): C, 43.73; H, 4.00; N, 4.64. Found: C, 43.82; H, 3.89; N, 4.57.

***N*-Boc-β-(4-Bromobenzyl)aspartic Acid (I).** This compound was prepared from β-(4-bromobenzyl)aspartate (20 g) by the Me_2SO method[10] and crystallized from ether–petroleum ether: yield 20.4 g (77%); mp 128.5–130 °C; TLC (CA) R_f 0.43; $[\alpha]^{24}D$ −15.5° (*c* 2.08, DMF).

Anal. Calcd for $C_{16}H_{20}BrNO_6$ (402.25): C, 47.77; H, 5.01; N, 3.48. Found: C, 47.85; H, 4.88; N, 3.74.

***N*-Boc-*O*-(4-Bromobenzyl)serine Dicyclohexylamine Salt (II).** The alkylation of *N*-Boc-serine hydrate (4.0 g, 18 mmol) with 4-bromobenzyl bromide was carried out as described by Hruby and Ehler.[11] After removal of the liquid ammonia the residue was shaken in a mixture of 100 ml of saturated aqueous NaCl, 10 ml of water, and 100 ml of ethyl acetate. The aqueous layer was discarded. To the ethyl acetate layer was added water (50 ml) and, while cooling and stirring, 3 N HCl was added to pH ca. 2. The ethyl acetate layer was washed with two 100-ml portions of water and dried over anhydrous $MgSO_4$. Removal of drying agent and solvent gave an oil (4.3 g) which was dissolved in ether (20 ml) and mixed with dicyclohexylamine (2.5 ml, 12.8 mmol). Removal of the ether gave a solid which was collected with use of petroleum ether: 5.3 g. This was dissolved in $CHCl_3$ (20 ml), evaporated in vacuo to an oil, and crystallized from ether–petroleum ether: 4.3 g (43%); mp 147–149 °C; $[\alpha]^{24}D$ +23° (*c* 2.2, $CHCl_3$).

Anal. Calcd for $C_{27}H_{43}BrN_2O_5$ (555.57): C, 58.37; H, 7.80; N, 5.04. Found: C, 58.83; H, 8.15; N, 5.32.

***O*-(4-Chlorobenzyl)threonine 4-Chlorobenzyl Ester Hydrogen Oxalate.** This compound was prepared as with the corresponding benzyl derivative[12] except that 4-chlorobenzyl alcohol (from reduction of 4-chlorobenzaldehyde with $NaBH_4$) was used. The crude product from 21.3 g (179 mmol) of threonine was crystallized from 8 l. of absolute ethanol: 20.5 g (25% yield); mp 192–193.5 °C; $[\alpha]^{24}D$ −67° (*c* 1.18, 80% acetic acid).

Anal. Calcd for $C_{20}H_{21}Cl_2NO_7$ (458.29): C, 52.42; H, 4.62; N, 3.06. Found: C, 52.17; H, 4.67; N, 3.23.

***N*-Boc-*O*-(4-Chlorobenzyl)threonine Dicyclohexylamine Salt (III).** The hydrogen oxalate salt just described (25.5 g, 55.6 mmol) was carried through the same procedure for the benzyl derivative. The resulting crude oil (20 g) was dissolved in ether (200 ml), mixed with dicyclohexylamine (12 ml), and allowed to crystallize at room temperature: 22 g. A portion (15.6 g) was dissolved in $CHCl_3$ (50 ml), evaporated in vacuo to an oil which was quickly dissolved in ether (200 ml), and allowed to crystallize: 15.0 g. The process was repeated with 400 ml of ether to give 14.0 g (68% yield): mp 150–153 °C; $[\alpha]^{24}D$ +26.5° (*c* 2, $CHCl_3$).

Anal. Calcd for $C_{28}H_{45}ClN_2O_5$ (525.03): C, 64.05; H, 8.63; N, 5.33; Cl, 6.75. Found: C, 63.84; H, 8.47; N, 5.18; Cl, 6.82.

Optical Purity of Derivatives. Samples of I, II, and III (1.0 mmol of each) were each treated in HF (20 ml) for 30 min at 0 °C in the presence of anisole (1.5 ml). After removal of HF, the residue was dissolved in 1 N HCl (20 ml), washed with two 20-ml portions of ether, and evaporated in vacuo to dryness. Quantitative amino acid analyses[13] gave yields of 100, 102, and 97% for aspartic acid, serine, and threonine, respectively. Optical rotation in 5 N HCl at 24 °C gave +24 (*c* 2.6), +14 (*c* 2), and −14° (*c* 2.4), respectively [lit.[14] $[\alpha]^{25}D$ (*c* 2, 5 NHCl) +25.4, +15.1, and −15°, respectively].

N-Boc-β-(4-BrBzl)Asp-OH, *N*-Boc-*O*-(4-BrBzl)Ser-OH, and *N*-Boc-*O*-(4-ClBzl)Thr-OH were coupled to H_2N-Phe-resin by in situ anhydride coupling[15] with 4 equiv of Boc-amino acid and 2.5 equiv of DCC in CH_2Cl_2 for 2.5 h at 24 °C. The corresponding dipeptides were obtained by treatment with HF (30–45 min at 0 °C) in the presence of anisole. Each dipeptide (2 μmol) was treated in 0.25 ml of 0.05 M Tris buffer of pH 8 (0.01 M Mg^{2+}) with 12 μg of leucineaminopeptidase (Worthington) for 24 h at 37 °. Quantitative amino acid analyses of the digests gave for H-Asp-Phe-OH, $Asp_{1.00}Phe_{0.95}$; for H-Ser-Phe-OH, $Ser_{0.95}Phe_{1.00}$; for H-Thr-Phe-OH, $Thr_{1.00}Phe_{0.97}$. The dipeptides H-Asp-Phe-OH and H-Ser-Phe-OH were separable from their constituent amino acids by TLC (BAW). The dipeptide H-Thr-Phe-OH was separable from its constituent amino acids by paper electrophoresis at pH 3.7 (pyridine acetate buffer). Each digest showed less than 1% of unhydrolyzed dipeptide by these criteria.

Stabilities of Protecting Groups in TFA and HF. The following reference derivatives were prepared by treatment of Ia, IIa, and IIIa in liquid HF for 15 min at 0 °C.

N-Acetylisoasparagine (3-acetaminosuccinamic acid, Ib), mp 165–167 °C. Anal. Calcd for $C_6H_{10}N_2O_4$ (174.16): C, 41.38; H, 5.79; N, 16.09. Found: C, 41.44; H, 5.75; N, 15.96.

N-Acetylserineamide (IIb), mp 141–143 °C. Anal. Calcd for $C_5H_{10}N_2O_3$ (146.15): C, 41.09; H, 6.90; N, 19.17. Found: C, 41.18; H, 6.85; N, 19.11.

N-Acetylthreonineamide (IIIb), mp 123–125 °C. Anal. Calcd for $C_6H_{12}N_2O_3$ (160.17): C, 44.99; H, 7.55; N, 17.49. Found: C, 45.03; H, 7.48; N, 17.49.

Samples (10 mg) of Ia, IIa, and IIIa were treated in 50% TFA in CH_2Cl_2 (10 ml, 24 °C, 71 h) and in liquid HF (5 ml containing 0.1 ml of anisole, 0 °C, 10 min). After removal of solvents by evaporation below reaction temperatures, the resulting products were dissolved in glacial acetic acid and run on TLC (BAW). The derivatives Ia, IIa, and IIIa all traveled with R_f's close to 0.70. The derivatives Ib, IIb, and IIIb gave R_f's of 0.29, 0.36, and 0.45, respectively. Estimates of side-chain removal in TFA or HF were made on TLC by running the treated derivatives along with serial aliquots of appropriate untreated derivatives and comparing color intensities revealed by chlorine–tolidine reagent.

Acknowledgment. The author wishes to thank Professor C. H. Li for his interest and encouragement and K. Hoey and

W. F. Hain for skilled technical assistance. This work was supported in part by U.S. Public Health Service Grant GM-2907.

Registry No.—I, 60803-65-8; Ia, 60803-66-9; Ib, 60803-67-0; II, 60803-69-2; IIa, 60803-70-5; IIb, 23361-38-8; III, 60803-72-7; IIIa, 60803-73-8; IIIb, 60828-33-3; β-(4-bromobenzyl) aspartate, 60828-77-5; *N*-Boc-serine, 3262-72-4; 4-bromobenzyl bromide, 589-15-1; dicydohexylamine, 101-83-7; *O*-(4-chlorobenzyl)threonine 4-chlorobenzyl ester hydrogen oxalate, 60803-75-0; chlorobenzyl alcohol, 873-76-7; H_2N-Phe, 63-91-2; H-Asp-Phe-OH, 13433-09-5; H-Ser-Phe-OH, 16875-28-8; H-Thr-Phe-OH, 16875-27-7.

References and Notes

(1) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(2) D. Yamashiro, R. L. Noble, and C. H. Li in "Chemistry and Biology of Peptides, Proceedings of the Third American Peptide Symposium", J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 197.
(3) B. W. Erickson and R. B. Merrifield in ref 2, p 191.
(4) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 98 (1957).
(5) Symbols and abbreviations are in accordance with the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **11**, 1726 (1972). Other abbreviations used follow: DCC, *N,N*^{1}-dicyclohexylcarbodiimide; Me_2SO, dimethyl sulfoxide; TFA, trifluoroacetic acid.
(6) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967); J. Lenard and A. B. Robinson, *J. Am. Chem. Soc.*, **89**, 181 (1967).
(7) B. Gutte and R. B. Merrifield, *J. Am. Chem. Soc.*, **91**, 501 (1969).
(8) R. S. Feinberg and R. B. Merrifield, *J. Am. Chem. Soc.*, **97**, 3485 (1975).
(9) R. Ledger and F. H. C. Stewart, *Aust. J. Chem.*, **18**, 1477 (1965).
(10) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969, p 29.
(11) V. J. Hruby and K. W. Ehler, *J. Org. Chem.*, **35**, 1690 (1970).
(12) T. Mizoguchi, G. Levin, D. W. Woolley, and J. M. Stewart, *J. Org. Chem.*, **33**, 903 (1968).
(13) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(14) J. P. Greenstein, *Adv. Protein Chem.*, **9**, 121 (1954).
(15) J. Rebek and D. Feitler, *J. Am. Chem. Soc.*, **96**, 1606 (1974).

A Convenient Total Synthesis of (±)-(7*E*,9*E*)-Trisporic Acid B Methyl Ester

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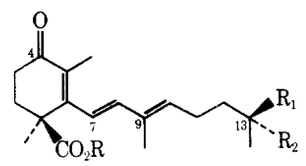
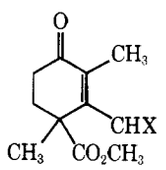
Received July 7, 1976

A brief converging total synthesis of the title compound is reported, utilizing as the key step a Michael-aldol sequence on the β-keto ester **4b** to form the highly functionalized cyclohexenone **2b.**

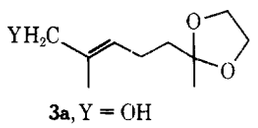
The sexual cycle of the fungi *Blakeslea trispora* and *Mucor mucedo* is mediated by a series of hormones, the trisporic acids (**1a–c,** R = H).[2] These hormones are derived biosynthetically from β-carotene,[3] and recently several prohormones have been isolated with lower oxidation levels at C-4 and the carboxylic acid carbon,[4] indicating that these are the sites of last modification in the biosynthesis. Synthetic efforts have thus far resulted in two syntheses of methyl trisporate B (**1b,** R = CH_3) and/or C (**1c,** R = CH_3),[5,6] and some work has recently been carried out on the utilization of Hagemann's ester for the formation of a potential intermediate in trisporic acid synthesis.[7] We wish to describe a convenient converging synthesis of the methyl ester of (±)-(7*E*,9*E*)-trisporic acid B (**1b,** R = CH_3), which is also a fully active compound.[4]



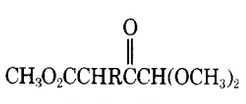
1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = O$ (and 9-cis)
c, $R_1 = H$; $R_2 = OH$ (and 9-cis)



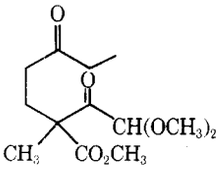
2a, X = O
b, $X = (OCH_3)_2$



3a, Y = OH
b, Y = Br
c, $Y = {}^+PPh_3{}^-$



4a, R = H
b, $R = CH_3$



5

The striking feature of this molecule is certainly the cyclohexenone moiety, suggesting a Michael-aldol sequence for its formation. We felt that the potential power of this sequence dictated its use, but contrary to previous work,[5,6] we wished to carry out the formation of the ring as quickly as possible, before the appendage at C-6 was attached. With this in mind we chose as our target molecules the aldehyde **2a** and the phosphonium salt **3c,** which we planned to join via a Wittig reaction. The choice of **2a** and **3c** provides us with two molecules each of which should be available in a few steps, thus portending a very direct overall route.

Analysis of the aldehyde **2a** indicates that the most effective means of applying the Michael-aldol sequence is to form the six-membered ring by joining a four-carbon unit to a two-carbon unit. Treatment of pyruvaldehyde dimethyl acetal with sodium hydride and dimethyl carbonate afforded the β-keto ester **4a,**[8] which was methylated with sodium hydride and methyl iodide to provide **4b.**[8] At this point there were several options available to us for the conversion to **2b.** In principle the Michael adduct might be first isolated, and then cyclized to **2b** under mild conditions, or the entire Michael-aldol sequence might be carried out at one time with a somewhat stronger base. The highly functionalized nature of **4b** suggested the former approach as the more promising one. Treatment of a solution of **4b** in methanol containing a catalytic amount of sodium methoxide with ethyl vinyl ketone did indeed afford **5,** which could be cyclized under various conditions to **2b.** More conveniently, however, the best procedure turned out to involve treatment of a solution of **4b** in methanol containing 1 equiv of sodium methoxide at room temperature with ethyl vinyl ketone over 3 h. This method provided **2b** directly in 45–50% yield, with no contamination by **5.** In this procedure methyl vinyl ketone also worked well as the Michael