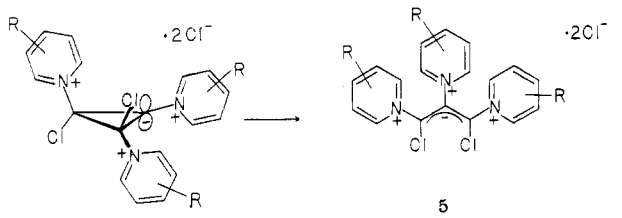
Table I. NMR Comparisons of 1 and 2 with Indolizine

	chemical shift, ppm				coupling constants, Hz					
	H_5	H_6	H_4	H_8	5,6	5,7	5,8	6,7	6,8	7,8
indolizine[a]	7.76	6.31	6.50	7.25	6.8	1.0	1.2	6.4	1.0	8.9
2	8.21	7.05	7.18	7.63	7.0	0.9		6.5	1.1	9.2
1	8.33	7.15	7.32	7.51	7.1	0.9		6.9	0.9	9.1

[a] Black, P. J.; Heffernon, M. L.; Jackman, L. M.; Porter, Q. N.; Underwood, G. R. *Aust. J. Chem.* **1964**, *17*, 1128.

Scheme I



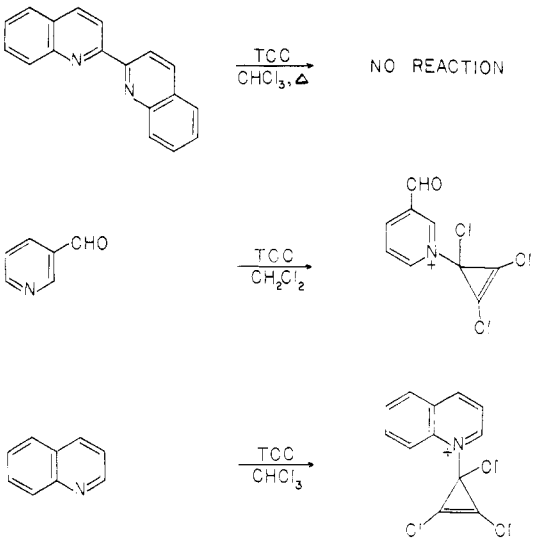
5

H_8 (δ 7.22, br s); H_5 (δ 8.20, d of d); $J_{5,6}$ = 7.7, $J_{6,8}$ = 1.1, $J_{5,8}$ = 1.0].

The pattern of substitution about the pyrrole part of the indolizine nucleus was ascertained indirectly by comparing the relative chemical shifts of indolizine protons as one proceeds from the parent unsubstituted indolizine to the monopyridinium system, **2**, and the bis(pyridinium) structure, **1** (Table I). The relatively symmetric Δ shifts of proton pairs, H_5, H_8, and H_6, H_7, in **2** suggest that the pyridinium is at the most nearly symmetric or 2-position. The anomalous (somewhat upfield) Δ shift of H_8 in **1** argues for the second pyridinium to be in the 1-position and interacting so as to deshield the peri proton. Single-crystal X-ray analysis of **2** confirms the assigned structure.[4]

In addition to producing indolizines possessing substituents that are either unknown (pyridinium) or rare (Cl on the pyrrole ring),[5] the reaction is interesting mechanistically. The limiting reagent is pyridine, and the combined yield of **1** and **2** based on TCC is essentially quantitative. The major product under all conditions is **1**; the ratio, **1**/**2**, varies only slightly, 3.5–5.0,[6] over a wide range of reactant ratios. Pyridines having electron-donating substituents produce indolizines unless both positions 2 and 6 of the pyridine are blocked, as in 2,6-lutidine and 2,4,6-collidine. A reaction occurs between these substrates and TCC but it is qualitatively much slower and indolizines are not isolated. The dark solids that are produced are insoluble in organic solvents and appear to react with water. We propose that these products are the corresponding allylic systems, **5**, and that **5** is an intermediate (R = H) in the reaction with pyridine itself. These suggestions are now being investigated as part of a general study of reaction mechanism including reaction kinetics.[7] Compound **5** is a novel allyl nitrogen ylid that is assumed to arise from the sequential addition of pyridine to TCC followed by electrocyclic ring-opening of the tris(pyridinium) cyclopropyl anion (Scheme I). Such substitution reactions of TCC are well-known with nucleophilic species.[8] The electrocyclic ring closure of pyridinium *N*-allylides to the indolizine ring structure has been documented.[9]

Pyridines with electron-withdrawing groups or heterocycles with electron-deficient nitrogens either do not react or yield the corresponding monosubstituted products, (trichlorocyclopropenyl)pyridinium chlorides. These salts apparently do not rearrange to trichloroindolizine derivatives. Typical examples are shown in the following reactions.



Acknowledgment. This research was supported in part by NSF Grant No. CHE 82-05696.

Registry No. **1**·2Cl⁻, 86289-23-8; **2**·BPh_4^-, 86289-25-0; **3**, 86289-26-1; **4**, 86289-27-2; **5**·2Cl⁻ (R = H), 86289-28-3; TCC, 6262-42-6; pyridine, 110-86-1; 3-pyridinecarboxaldehyde, 500-22-1; quinoline, 91-22-5; 1-(3-trichlorocyclopropenyl)pyridinium-3-carboxaldehyde chloride, 86289-29-4; 1-(3-trichlorocyclopropenyl)quinolinium chloride, 86289-30-7.

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(4) Smith, K. A.; Hollander, F.; Streitwieser, A., Jr., manuscript in preparation.
(5) Berg-Nielsen, K. *Acta Chem. Scand., Ser. B.* **1977**, *31*, 224. Ohsawa, A.; Abe, Y.; Igeta, H. *Chem. Lett.* **1979**, 241–4.
(6) Determined by NMR of chlorides. Isolated yields of **2** as the tetraphenylborate were lower because of repeated recrystallization to remove pyridinium tetraphenylborate.
(7) Waterman, K. C., unpublished results.
(8) Yoshida, Z. *Top. Curr. Chem.* **1973**, *40*, 47.
(9) Sasaki, t.; Kanematsu, K.; Kakehi, A.; Ito, G. *Tetrahedron* **1972**, *28*, 4947. Pohjala, E. *Tetrahedron Lett.* **1972**, 2585.

An Efficient Synthetic Route to (±)-Nanaomycin A

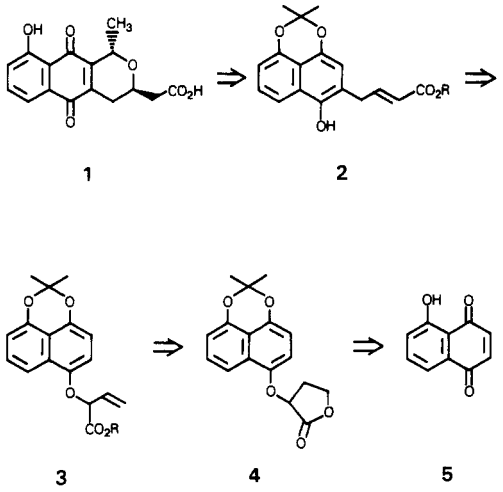
Summary: An efficient synthetic route to (±)-nanaomycin A (**1**) involving a new type of Claisen rearrangement is described.

Sir: Nanaomycin A (**1**), a member of the family of pyrananaphthoquinone antibiotics, exhibits significant antimicrobial activity[1] and also bears potential antineoplastic activity.[2] The total synthesis of **1** has recently been a

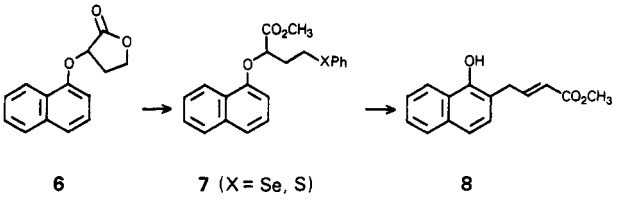
(1) (a) Omura, S.; Tanaka, H.; Koyama, Y.; Oiwa, R.; Katagiri, M.; Awaya, J.; Nagai, T.; Hata, T. *J. Antibiot.* **1974**, *27*, 363. (b) Tanaka, H.; Koyama, Y.; Awaya, J.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *Ibid.* **1975**, *28*, 860. (c) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Omura, S. *Ibid.* **1975**, *28*, 868.

0022-3263/83/1948-2630$01.50/0

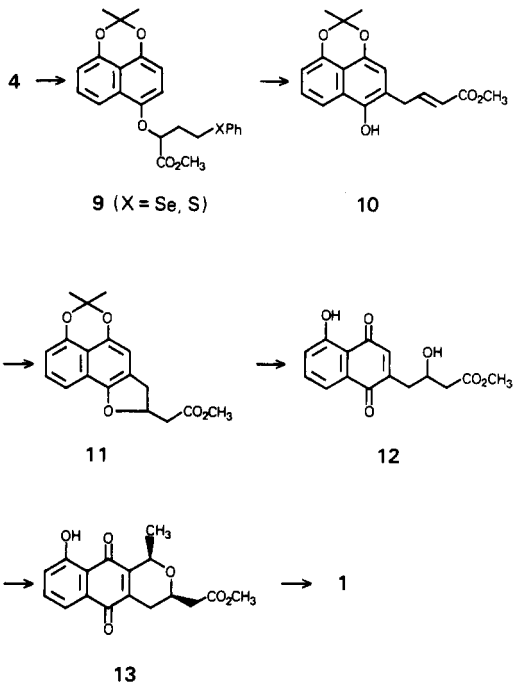
Scheme I



Scheme II



Scheme III



subject of considerable interest, yielding several elegant approaches.[3] All of the reported syntheses, including ours, however, seem impractical in the sense of multigram preparations of the antibiotic. In this communication we introduce a convenient and efficient synthetic route to (±)-1, starting with juglone (5), which is now readily available.

The synthetic strategy outlined in Scheme I required a new method for the regiospecific introduction of the 2-butenoate side chain to the juglone structure by a variant of the Claisen rearrangement (3 → 2). The reasonable precursor of 3 should be the butyrolactone 4. In order to test the feasibility of the proposed transformation 4 → 2, we first carried out a model experiment dealing with 1-naphthol (Scheme II).

Reaction of 1-naphthol with α-bromo-γ-butyrolactone in acetonitrile in the presence of KF-Celite[4] at 60 °C for 6 h afforded α-(naphthyloxy)-γ-butyrolactone (6),[5] mp 76–77 °C, in 92% yield. The lactone 6 was then subjected to nucleophilic alkyl–oxygen bond cleavage with sodium phenylselenolate[6] in DMF at 120 °C followed by esterification with diazomethane produced the carboxylic acid methyl ester 7 (X = Se),[5] bp 150–155 °C at 0.5 torr, in 89% yield. When 7 (X = Se) was treated with hydrogen peroxide[7] in THF at room temperature for 3 h and the oxidation product was heated at 90 °C under reduced pressure (ca. 20 torr) for 1 h, the desired rearrangement product 8,[5] mp 109–110 °C, was obtained in 76% yield after silica gel chromatography. Use of the thio analogue was also attempted. Thus, reaction of 6 with PhSNa in DMF at 120 °C and esterification of the resulting carboxylic acid afforded 7 (X = S),[5] bp 200–210 °C at 1.0 torr, in 88% yield. Oxidation of the latter compound with MCPBA[8] in CH_2Cl_2 at 0 °C followed by thermolysis at 200 °C gave 8 in 59% yield.

With the new effective ortho(3-alkoxycarbonyl)allylation of naphthol thus established, we were encouraged to apply the methodology to the synthesis of nanaomycin A. Juglone (5), which was obtained by salcomine-catalyzed air oxidation of naphthalene-1,5-diol (ca. 60% yield on a large scale)[9] was readily transformed to 4,[5] bp 200–210 °C at 1.0 torr, in 74% yield by the following sequence of reactions without purification of the intermediates: sodium hydrosulfite reduction (AcOEt–H_2O system/10 min), acetonide formation with 2,2-dimethoxypropane (acetone/

(2) Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527.

(3) (a) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*, 4382. (b) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850. (c) Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 609. (d) Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191. (e) Kometani, T.; Takeuchi, Y.; Yoshii, E. *Ibid.* **1981**, 1197. (f) Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, *21*, 4469. (g) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923. (h) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263. (i) Pyrek, J. St.; Achmatowica, O., Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673.

(4) Ando, T.; Yamawaki, J. *Chem. Lett.* **1979**, *45*.

(5) All new compounds have been fully characterized by IR, ^1H NMR, and mass spectroscopies, and elemental composition has been established by combustion analysis and/or high-resolution mass spectroscopy. **4**: IR (neat) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (3 H, s), 1.60 (3 H, s), 2.40–2.75 (2 H, m), 4.20–4.60 (2 H, m), 4.91 (1 H, t, J = 8 Hz), 6.64 (1 H, d, J = 8 Hz), 6.80 (1 H, d, J = 8 Hz), 6.93 (1 H, d), 7.33 (1 H, t, J = 8 Hz), 7.66 (1 H, d, J = 8 Hz); MS, m/e (relative intensity) 300 (M^+, 44), 215 (100), 176 (25), 174 (47). **9** (X = Se): IR (neat) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (6 H, s), 2.20–2.60 (2 H, m), 3.15 (2 H, t, J = 7 Hz), 3.68 (3 H, s), 4.92 (1 H, dd, J = 8, 5 Hz), 6.58 (1 H, d, J = 8 Hz), 6.70 (1 H, d, J = 8 Hz), 6.92 (1 H, d, J = 8 Hz), 7.15–7.60 (6 H, m), 7.94 (1 H, d, J = 8 Hz). **9** (X = S): IR (neat) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (6 H, s), 2.15–2.50 (2 H, m), 3.13 (2 H, t, J = 7 Hz), 3.64 (3 H, s), 4.85 (1 H, dd, J = 7, 5 Hz), 6.55 (2 H, br s), 6.80 (1 H, d, J = 8 Hz), 7.40–7.43 (6 H, m), 7.74 (1 H, d, J = 8 Hz); MS, m/e (relative intensity) 424 (M^+, 84), 214 (64), 208 (100). **10**: ^1H NMR ($CDCl_3$) δ 1.60 (6 H, s), 3.63 (2 H, m), 3.69 (3 H, s), 5.56 (1 H, br s), 5.83 (1 H, dt, J = 15, 1.5 Hz), 6.60 (1 H, s), 6.83 (1 H, d, J = 8 Hz), 7.00–7.64 (3 H, m); MS, m/e (relative intensity) 314 (M^+, 100), 254 (76). **11**: IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (6 H, s), 2.72 (1 H, dd, J = 15, 7 Hz), 2.99 (1 H, dd, J = 15, 7 Hz), 3.08 (1 H, dd, J = 16, 7 Hz), 3.58 (1 H, dd, J = 16, 9 Hz), 5.10–5.60 (1 H, m), 6.72 (1 H, s), 6.81 (1 H, d), 7.30–7.50 (2 H, m); MS, m/e (relative intensity) 314 (M^+, 100), 254 (25). **12**: ^1H NMR ($CDCl_3$) δ 2.50–2.80 (4 H, m), 3.20 (1 H, br s), 3.75 (3 H, s), 4.30 (1 H, m), 6.95 (1 H, t, J = 2 Hz), 7.29 (1 H, m), 7.63 (2 H, m), 11.88 (1 H, s); MS, m/e (relative intensity) 290 (M^+, 5), 272 (15), 268 (29), 188 (100).

(6) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904.

(7) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(8) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(9) Wakamatsu, T.; Nishi, T.; Onuma, T.; Ban, Y. "Abstracts of Papers", 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, Japan, 1981; p 384.

BF_3–Et_2O/1 h), and treatment with α-bromo-γ-butyrolactone (DMF/CsF/120 °C/1 h[10] or KF-Celite/CH_3CN/60 °C/14 h). The lactone **4** was then reacted with PhSeNa by the same procedure as described for the model experiment to afford the phenylselenide **9** (X = Se)[5] in 81% yield after distillation (bp 210–220 °C at 0.1 torr) (Scheme III). Oxidative elimination of the phenylseleno group from **9** (X = Se) occurred readily again to give the rather unstable naphthylbutenoate **10**[5] in 72% yield, which on treatment with methanolic Na_2CO_3 was cyclized to yield the key dihydrofuran intermediate **11**,[5] bp 160–165 °C at 1.0 torr, in 91% yield (an overall yield of 54% from **4**). Similarly, transformation of **4** to **11** was carried out via the phenyl sulfide **9** (X = S)[5] in comparable yield.

Now, oxidative removal of the acetonide group of **11** with silver(II) oxide generated a 2-hydroxybutyrate side chain, giving the nanaomycin A precursor **12**, mp 87–88 °C, in 80–90% yield. Formation of the dihydropyran ring was then achieved according to the method of Li,[3h,i] i.e., reaction of **12** with zinc and hydrochloric acid in THF for 5 min, addition of excess acetaldehyde to the reaction mixture and heating at 60 °C for 4 h, and oxidation of the resulting product with silver(I) oxide. The pyranojuglone **13** (cis isomer of nanaomycin A methyl ester) obtained in 51% yield was identified by comparison of the spectral data with those of the authentic sample synthesized by an alternative route by us.[3e] Isomerization of **13** to the trans isomer with sulfuric acid followed by saponification[3c,h] afforded (±)-nanaomycin A in 66% yield.

The synthetic route to **1** has several advantages over the reported ones beginning with naphthalenediols.[3c,f,h] The highest overall yield has been achieved even though each step has not been optimized. Multigram quantities of the antibiotic can be prepared from commercially available reagents and in an operationally simple manner.

Registry No. (±)-**1**, 73804-47-4; (±)-**4**, 86309-79-7; **5**, 481-39-0; (±)-**6**, 86309-80-0; (±)-**7** (X = Se), 86309-81-1; (±)-**7** (X = S), 86309-82-2; **8**, 86309-83-3; (±)-**9** (X = Se), 86309-84-4; (±)-**9** (X = S), 86309-85-5; **10**, 86309-86-6; (±)-**11**, 86309-87-7; (±)-**12**, 86309-88-8; (±)-*cis*-**13**, 78340-70-2; (±)-*trans*-**13**, 73804-46-3; 1-naphthol, 90-15-3; (±)-α-bromo-γ-butyrolactone, 86362-17-6; 1,4,5-naphthalenetriol, 481-40-3; 1,4,5-naphthalenetriol 4,5-acetonide, 86309-89-9; acetaldehyde, 75-07-0.

(10) Clark, J. H.; Miller, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 498.

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Facile Bridged Bicycloalkane Synthesis via Intramolecular Nitrone-Olefin Cycloaddition

Summary: Exocyclic nitrones smoothly participate in intramolecular cycloaddition reactions to provide bridged bicycloalkanes. The application of this methodology in the first total synthesis of the antifertility agent (±)-7,12-secoishwaran-12-ol is also discussed.

Sir: The development of effective approaches to bridged bicycloalkanes is an important topic in organic synthesis.[1]

Scheme I

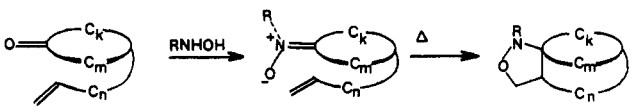
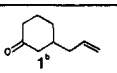
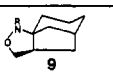
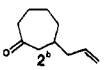
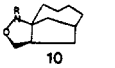
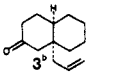
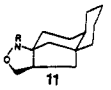
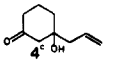
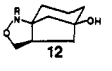
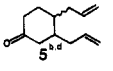
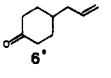
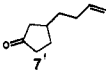
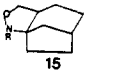
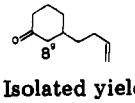
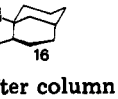


Table I. Cyclizations of Alkenylcycloalkanones Mediated by Alkylhydroxylamines

cycloalkanone	bridged bicycloalkane	temp, °C/ time, h	yield,[a] % (R)
		80/3	84 (Me) 100 (Bz) 74 (Ph)
		80/3	84 (Me) 82 (Bz)
		80/2	94 (Bz)
		80/3	66 (Me) 70 (Bz)
		80/5	75 (Me) 90 (Bz)
		111/36	48 (Bz)
		111/24	50 (Bz)
		111/48	46 (Me)

[a] Isolated yield after column chromatography. [b] Prepared by adding allyltrimethylsilane to the corresponding cycloalkenone in the presence of $TiCl_4$ as described by: Sakurai, H.; Hosomi, A. *J. Am. Chem. Soc.* **1977**, *99*, 1673. [c] Prepared by addition of excess allylmagnesium bromide to the sodium enolate of cyclohexane-1,3-dione (20%). [d] Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. [e] Conia, J. M.; Moinet, G. *Bull Soc. Chim. Fr.* **1969**, 500. [f] Conia, J. M.; Beslin, P. *Ibid.* **1969**, 483.

This structural type is manifest in a wide variety of natural products. In addition, the fragmentation or rearrangement of bridged bicycloalkanes is an established protocol for the synthesis of other ring systems.[2] We now describe a new approach to bridged bicycloalkanes and document the potential of this methodology in the first total synthesis of the antifertility agent (12*S*)-7,12-secoishwaran-12-ol.[3]

(1) A particularly novel approach to these ring systems has been reported recently and underscores the continuing interest in this area: Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784.

(2) Some notable examples include the following. (a) Bicyclo[2.2.1]-heptane → prostaglandins E_2 and $F_{2\alpha}$: Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Bicyclo[2.2.1]heptane → ambrosin and damsin: Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *Ibid.* **1982**, *104*, 4226. (c) Bicyclo[2.2.2]octane → trichodermol: Still, W. C.; Tsai, M.-Y. *Ibid.* **1980**, *102*, 3654. (d) Bicyclo-[2.2.2]octane → eriolanin: Roberts, M. R.; Schlessinger, R. H. *Ibid.* **1981**, *103*, 724. (e) Bicyclo[3.2.1]octane → hinesol: Marshal, J. A.; Brady, S. F. *Tetrahedron Lett.* **1969**, 1387. (f) Bicyclo[3.3.1]nonane → ophiobolin ring system: Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *42*, 3633. (g) Bicyclo[4.3.1]decane → bulnesol: Marshal, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090.

(3) (a) Pakrashi, A.; Chakrabarty, B.; Dasgupta, A. *Experientia* **1976**, *32*, 394. (b) Pakrashi, S. C.; Ghosh Dastidur, P. P.; Basu, S.; Achari, B. *Phytochemistry* **1977**, *16*, 1103. (c) Pakrashi, A.; Shaha, C. *Experientia* **1977**, *33*, 1498. (d) Pakrashi, S. C.; Ghosh Dastidur, P. P.; Chakrabarty, S.; Achari, B. *J. Org. Chem.* **1980**, *45*, 4765.

0022-3263/83/1948-2632$01.50/0