and the aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried (Na_2SO_4), the solvent mixture was evaporated at reduced pressure (bath temperature 20–25 °C), and the last traces of pyridine were removed from the residue by repeated co-distillation with benzene. The residue (0.45 g) was purified by dry-column chromatography on silica gel (50 g). Elution was started with benzene (250 mL), followed by $CHCl_3$ to yield 0.37 g (85%) of the oily tosylate **4**, which was not further purified: IR ($CHCl_3$) 3600, 1360, 1170, 880 cm^{-1}; NMR δ 0.3–2.0 (m, 11 H, norcarane), 2.45 (s, 3 H, $-CH_3$), 3.0–3.3 (m, 1 H, –CHOH–), 3.8–4.25 (m, 2 H, $-CH_2OTs$), 7.3–7.9 (q, 4 H, aromatic); mass spectrum *m/e* 292 ($M^+ - H_2O$).

***exo*-(7-Bicyclo[4.1.0]heptyl)oxirane (5).** To the solution of crude tosylate **4** (8.1 g, 26 mmol) in dry glyme (150 mL) KOH pellets (3.5 g, 62.5 mmol) were added and the mixture was stirred magnetically at room temperature for 0.5 h, when TLC showed disappearance of the starting material. After filtration and evaporation of the solvent under reduced pressure, the residue was distilled to yield the oxirane **5** (3.1 g, 86%): bp 96–98 °C (20 mm); NMR δ 0.4–2.2 (m, 11 H, bicycloheptane ring protons), 2.3–2.8 (m, 3 H, epoxide ring protons); mass spectrum *m/e* 138.1049 (M^+ calcd for $C_9H_{14}O$: 138.10446).

***exo*-7-Vinylbicyclo[4.1.0]heptane (6).** A mixture of the diol **2** (1.87 g, 12 mmol) and *N,N'*-thiocarbonyldiimidazole[9] (2.03 g, 12 mmol) in dry toluene (25 mL) was heated at reflux for 1 h under N_2. The solvent was then removed, water (50 mL) was added, and the mixture was extracted with ether. The product, isolated from the ether solution, was purified by dry-column chromatography on silica gel. Elution with hexane–benzene (1:1) gave 1.43 g (52%) of oily thionocarbonate **3**: IR ($CHCl_3$) 1285 cm^{-1}; NMR δ 0.6–2.1 (m, 11 H, bicycloheptane ring protons), 4.2–4.8 (m, 3 H, five-membered ring protons); mass spectrum *m/e* 198 (M^+).

A mixture of the above thionocarbonate **3** (1.98 g, 10 mmol) and freshly distilled trimethyl phosphite (4 mL) was heated at reflux for 30 h under N_2. Excess of trimethyl phosphite was removed by distillation at 110–120 °C (760 mm), and the residue was distilled at 70–75 °C (28 mm) to yield 1.0 g (85%) of **6** contaminated with traces of trimethyl phosphite (NMR). An analytical sample was obtained by VPC (3% SE 30 on 100–120 mesh Chromosorb Q at 80 °C): IR ($CHCl_3$) 1630 cm^{-1} (C=C); NMR δ 0.7–2.2 (m, 11 H, bicycloheptane ring protons), 4.6–5.1 (m, 2 H, $-H_AC{=}CH_BH_C$), 5.1–5.7 (m, 1 H, H_A) (J_{AB} = 19, J_{AC} = 12, J_{BC} = 2 Hz); NMR spectrum was identical with that of an authentic sample of the exo isomer.[2]

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C,88.34; H, 11.47.

Lead Tetraacetate Oxidation of Diol 2. The diol **2** (0.39 g, 2.5 mmol) was oxidized with $Pb(OAc)_4$ (1.27 g, 2.8 mmol) in dry benzene (30 mL) at room temperature by the method described for the oxidation of *exo*-(7-bicyclo[4.1.0]heptyl)glycolic acid.[3] The resulting aldehyde was further oxidized with Ag_2O to give the known *exo*-bicyclo[4.1.0]heptane-7-carboxylic acid (0.3 g, 85%): mp 97–98 °C (lit.[10] mp 97–99 °C); IR ($CHCl_3$) 1690 cm^{-1}; NMR δ 1.08–2.17 (m, 11 H); 12.1 (s, 1 H, –COOH); mass spectrum *m/e* 140 (M^+).

Ozonation of Olefin 6. Ozone was bubbled through an ice-cold magnetically stirred solution of olefin **6** (0.122 g, 1.0 mmol) in methylene chloride (20 mL). After the ozonation was completed (permanent blue color), the excess ozone was removed by passing nitrogen through the reaction mixture, and the solvent was removed under reduced pressure at low temperature.[11] To the residue acetone (A.R. Grade; 20 mL) was added and the magnetically stirred and cooled solution (ice bath) was titrated with Jones' reagent. After addition of water, the aqueous layer was extracted with methylene chloride (two 10-mL portions), and the combined organic layers were washed with saturated NaCl solution (20 mL), dried, and filtered. Evaporation of the solvent gave *exo*-bicyclo[4.1.0]heptane-7-carboxylic acid (0.13 g, 92%), identical with that obtained by the $Pb(OAc)_4$ oxidation of diol **2**.

Acknowledgment. We would like to thank Professor R. G. Salomon for providing the NMR spectra of *exo*- and *endo*-7-vinylbicyclo[4.1.0]heptanes for comparison.

Registry No.—**1**, 61558-26-7; **2**, 61558-30-3; **3**, 63076-63-1; **4**, 63076-64-2; **5**, 63076-65-3; **6**, 53951-19-2; *p*-TsCl, 98-59-9; *N,N'*-thiocarbonyldiimidazole, 6160-65-2; *exo*-bicyclo[4.1.0]heptane-7-carboxaldehyde, 4729-40-2; *exo*-bioyclo[4.1.0]heptane-7-carboxylic acid, 21448-77-1.

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(7) Melting points were taken in capillaries and are uncorrected. The IR spectra were determined on a Perkin-Elmer infrared spectrophotometer. NMR were recorded on a Varian T-60 or on a Varian A-60 spectrometer in $CDCl_3$ solution using Me_4Si as internal standard.
(8) The formation of this diol as a by-product in the $NaBH_4$ reduction of **1** was observed and described by us recently.[3]
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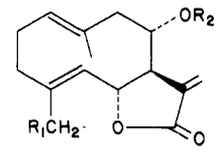
(11) Caution! Since ozonides are potentially dangerous, this operation should be carried out behind a safety shield.

Communications

An Approach to the Synthesis of Complex Germacranes. A New Route to Highly Functionalized 9-Methyl-1-decalones

Summary: Reductive C-methylation of α-tetralones in liquid ammonia provides a general, high-yielding procedure for the synthesis of 9-methyl-1-decalones suitable for the synthesis of germacranes and related sesquiterpenes.

Sir: Several ingenious approaches to the synthesis of the simpler germacranes have been reported.[1] The preparation of more complex representatives, e.g., tulipinolide (**1**)[2] and cnicin (**2**),[3] whose cytoxic properties have aroused considerable interest,[4] poses problems of a much greater magnitude.

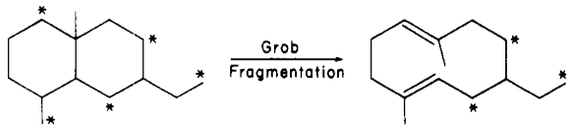


1 R_1=H, R_2=$COCH_3$

2 R_1=OH, R_2=$COC(CH_2)CH(OH)CH_2OH$

While the fragmentation of a suitable decalin derivative (Scheme I) with the oxygenation pattern indicated (*) in structure **3**[5] appeared to offer a possible method, this pattern of functionality does not arise readily from traditional decalin syntheses.[1,6] A novel approach was indicated. We report that the reductive alkylation of α-tetralone derivatives[7] offers a flexible and efficient entry to the synthesis of such decalins.

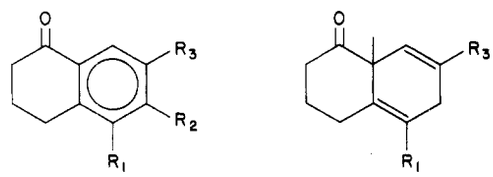
Scheme I



3

5-Methoxy-1-tetralone (4)[8] was reduced and methylated to give the dihydro derivative 7[9] in 93% yield by the procedure described below. Crucial to the success of the method are the regiospecific protonation at C-6 (brought about by using potassium and *tert*-butyl alcohol at low temperature) and regiospecific alkylation at C-9 (achieved by alkylating the *lithium* enolate).[7] Removal of ammonia before alkylation always resulted in the recovery of significant (up to 30%) quantities of tetralone **4**. When methylation was initiated in ammonia, overmethylation (apparently at C-2) occurred. The simultaneous addition of water to destroy *tert*-butoxide minimized this problem.[10]

The method cannot be used to prepare compounds with a C-6 oxygen function, since such groups undergo reductive elimination.[11] The loss of such a substituent, however, may be usefully exploited in the synthesis of suitable substrates. Cyclodehydration of 4-phenylbutyric acids is the most general method for the preparation of α-tetralones,[12] but, without a suitable activating substituent, yields are frequently poor. For example, 5,7-dimethoxy-1-tetralone cannot be made satisfactorily by this means.[13] The readily available 5,6,7-trimethoxy derivative **5**,[14] however, was converted in 93% yield to the 5,7-dimethoxy ketone **8**, bp[9] 130 °C (0.3 Torr) (an extra 2 equiv of potassium and 1 equiv of *tert*-butyl alcohol were required).[15] 6,7-Dimethoxytetralone (**6**)[16] was similarly converted to ketone **9**, bp[9] 110 °C (0.2 Torr).

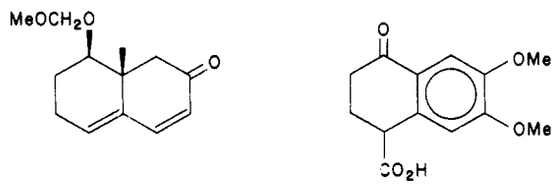


4 R_1 = OMe; R_2,R_3 = H ⟶ 7 R_1 = OMe; R_3 = H

5 R_1,R_2,R_3 = OMe ⟶ 8 R_1,R_3 = OMe

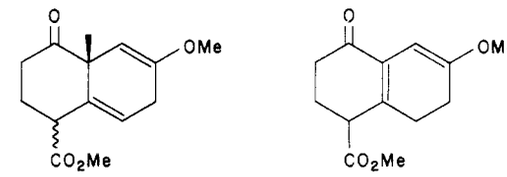
6 R_1 = H; R_2,R_3 = OMe ⟶ 9 R_1 = H; R_3 = OMe

Any of the decalones **7–9** readily affords the *B*-ring oxygenation pattern of general structure **3** by functional group manipulation. A C-4 substituent could, in principle, be introduced by 1,6 addition to dienone **10**, which was prepared in a simple sequence ($NaBH_4$ reduction, methoxymethylation,[17] hydrolysis, and DDQ oxidation[18]) from ketone **9**. We elected instead to incorporate a C-4 substituent into a tetralone substrate. Of the groups which could be carried through the cyclodehydration and the reductive alkylation, carboxyl appeared to be the most satisfactory. Thus, the carboxylic acid **11**, mp 160–161 °C, was prepared[19] and



10 11

subjected to the usual procedure, except that the ammonium ions generated by the addition of acid to the ammonia were neutralized with potassium *tert*-butoxide before reduction; otherwise, nonregiospecific protonation occurred. After methylation with diazomethane to facilitate handling, the two diastereomeric esters **12** (mp 123–125 °C, 64%) and **13** (mp 89–90 °C, 19%) were obtained. If the enolate was allowed to warm up before the methylation was performed, the labile, rearranged compound **14** was the major product.

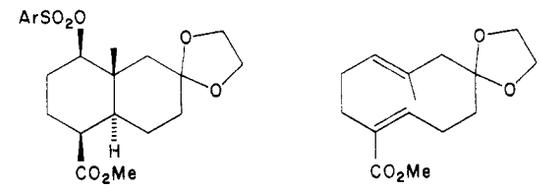


12 4α

13 4β

14

The esters **12** and **13** can in principle be converted to substrates of the general structure **3** by alkylation at C-6 and oxygenation at C-5. Their potential for germacrane synthesis is convincingly illustrated by the conversion of **13** to the tosylate **15** which, on treatment with lithium diisopropylamide in THF at 24 °C, was converted (half-life ~30 min) cleanly to the diene **16**. More generally, it is clear that the method is a valuable complement to standard annelation procedures and is appropriate to a wide variety of carbocyclic synthesis, notably in the terpenoid field.



15 16

Sample experimental procedures follow. A stirred solution of **4** (1.76 g, 10 mmol) and *tert*-butyl alcohol (1.88 mL, 20 mmol) in dry THF (10 mL) and dry ammonia (80 mL) under N_2 at −78 °C was treated with potassium metal (0.978 g, 25 mg atom), followed after 10 min by a solution of dry LiBr (2.14 g, 25 mmol) in dry THF (15 mL). After 20 min methyl iodide (3.1 mL, 50 mmol) and aqueous THF (1:1, 10 mL) were added simultaneously. The cooling bath was removed, the ammonia driven off, and water added. The mixture was extracted with ether, the extracts were washed with water and brine, and the solvent was removed. The residue was purified by column chromatography (Kieselgel 60, EtOAc–hexane 3:17) to give **7** (93%) as a colorless oil. An analytical sample was prepared by bulb-to-bulb distillation at 90 °C (0.3 Torr): IR (film) 1708 (s, C=O), 1655 cm^{-1} (ω, C=COMe); NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.5–3.4 (m, 6 H, H-2, H-3, H-4), 2.77 (2 H, m, H-6), 3.55 (s, 3 H, OCH_3), 5.67 (dt, 1 H, J = 3.5, 10 Hz, H-7), 5.96 (dt, 1 H, J = 2, 10 Hz, H-8). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.0; H, 8.4. Found: C, 75.1; H, 8.3%.

The preparation of **8** from **5** and **9** from **6** required 3 equiv of *tert*-butyl alcohol, 4.5 equiv of potassium, and 4.5 equiv of LiBr.

The conversion of **11** to **12** and **13** required addition to the original solution of 1.1 equiv of potassium *tert*-butoxide and the use of 3 equiv of *tert*-butyl alcohol, 4.5 equiv of potassium, and 5.6 equiv of LiBr. After removal of ammonia, addition of water, and removal of THF, the mixture was acidified with ice-cold 1 N HCl to pH 8, layered with chloroform, and further acidified to pH 3 with vigorous swirling. The organic solution was separated, washed twice with water, filtered (Whatman No. 1 PS), and treated with an excess of ethereal diazomethane.

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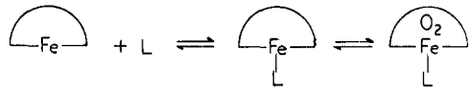
Efficient Peripheral Functionalization of Capped Porphyrins

Summary: An efficient method of functionalizing a capped porphyrin (**1**) is achieved by use of silver nitrite–iodine reagent. The nitro derivative is cleanly reducible to the amine, which may be further derivatized by standard procedures.

Sir: Previously we reported the synthesis of capped porphyrin **1** and the observation that its iron(II) complex exhibited reversible and stoichiometric binding of dioxygen at ambient temperature.[1,2] This reversible behavior was shown to be dependent on the concentration of apical ligand, L, e.g., *N*-methylimidazole, as a consequence of the equilibrium between irreversibly oxidized square planar form **2** and reversibly oxygenated pentacoordinate species **3**, eq 1. One obvious solution



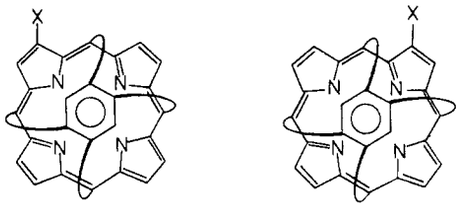
(1)

2 3 4

to the difficulties associated with working at high ligand concentrations was to attach the apical ligand L directly to the capped structure, schematically as **5**, thereby removing, at least in part, the preliminary equilibrium in eq 1. Similar reasoning has guided the experiments of others in this field.[3]

5

We now report an efficient direct peripheral functionalization of **1**, itself now available in quantity by a modification[4] of our original synthesis.[1] After many unsuccessful attempts at conventional electrophilic nitration procedures, we developed the following method. Thus the zinc-capped porphyrin, prepared by addition of anhydrous zinc chloride to a refluxing DMF solution of the free porphyrin[5] in CH_2Cl_2–CH_3CN (1:1), was treated sequentially with iodine (1.5 M, CH_2Cl_2) and silver nitrite (1.5 M, CH_3CN), stirred for 35 min at 25 °C, filtered, and evaporated to dryness.[6] Trituration with CH_2Cl_2 gave, after concentration, an approximately equal mixture of two isomeric zinc mononitroporphyrins as a purple solid (98%): M^+ 1143 ± 1; λ_{max} (CH_2Cl_2) 605, 558, 520 (sh), 431 nm; NMR ($CDCl_3$) δ 3.5–4.6 (m, 16 H), 5.03, 5.78 (d, 1 H), 5.43, 5.57 (d, 1 H), 7.17–8.0 (m, 16 H), 8.57–8.77 (m, 7 H).[7,8] Removal of the zinc (HBr gas, CH_2Cl_2, 5 min, 25 °C) gave the metal-free nitroporphyrin isomers **6** and **7**[8] as a crystalline solid (quantitatively) [M^+ 1143 ± 1; λ_{max} (CH_2Cl_2) 668, 605, 531, 425 nm; ν_{max} (KBr) 1723, 1510, 1342 cm^{-1}] which could be separated by preparative thin-layer chromatography over silica gel (C_6H_6–EtOAc, 7:3 v/v); however, for our present purposes, we have proceeded with this mixture.



6 + 7, X = NO_2
8 + 9, X = NH_2
10 + 11, X = $NHCOCH_3$
12 + 13, X = NCO
14 + 15, X = $NHCO_2CH_2CH_3$

Reduction of the nitro group was achieved in a clean and reproducible manner by addition of sodium borohydride (50 equiv) to a suspension of 10% Pd/C in a solution of the nitro-capped porphyrin in dried ch_2Cl_2–CH_3OH (1:1 v/v) under argon. After stirring (30 min), filtration and evaporation gave the unstable aminoporphyrins **8** and **9** in quantitative yield: λ_{max} (CH_2Cl_2) 651, 595, 560 (sh), 522, 425, 418; ν_{max} (KBr) 3420, 3350, 1725 cm^{-1}; NMR ($CDCl_3$) δ −3.21 (1 H), −2.72 (1 H), 3.8–4.7 (m, 16 H), 5.5, 5.6, 5.8, 5.95 (4s, 2 H), 7.2–7.8 (m, 16 H), 8.3–8.8 (m, 7 H). This substance is unstable to chromatography and is readily acetylated (pyr, Ac_2O) to the *N*-