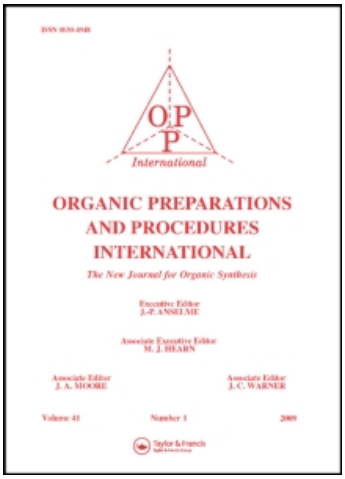

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SYNTHESIS OF β- AND γ-ALKOXY AND β-DIMETHYLAMINO 1- AND 2-SUBSTITUTED-1,3-CYCLOPENTADIENES

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SYNTHESIS OF β- AND γ-ALKOXY AND β-DIMETHYLAMINO 1- AND 2-SUBSTITUTED-1,3-CYCLOPENTADIENES

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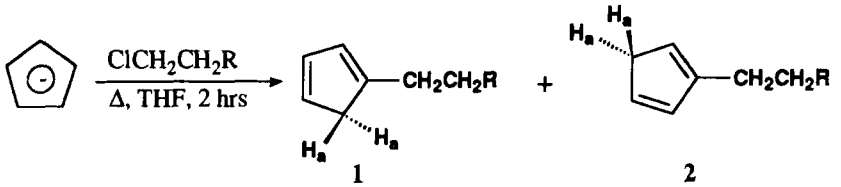
As part of our research effort directed at the preparation of volatile organometallic compounds of the group 2 elements Ca, Sr, and Ba,[1] we needed cyclopentadienide anions exocyclically β- or γ-substituted with ether or amine functionality capable of intramolecular coordination to the central metal atom. Although many ring-, and a few α-exocyclic heteroatom-substituted cyclopentadienes are known,[2] they were not useful to our need which required the presence of an alkylene chain linker between the cyclopentadiene and the heteroatom of appropriate length and flexibility to coordinate with the metal center.[3]

Compounds **1** and **2** were prepared as regioisomeric mixtures[4] by reaction of the appropriate primary alkyl chlorides with cyclopentadiene anion. Although reduced pressure distillation may be employed for all these purifications, it was necessary only for the complete purification of **1c, 2c**. All new regioisomeric mixtures of compounds were characterized by ^1H and ^{13}C NMR, low and high resolution MS, and combustion analyses. They have been utilized in the preparation of elementocene compounds of main group and transition elements.[5] Although not necessary in this instance, presumably, the regioisomers could be separated if desired.



1 **2**

a) R = OMe b) R = OEt c) R = CH_2OEt d) R = NMe_2

EXPERIMENTAL SECTION

All reactions were carried out following standard techniques for the manipulation of air-sensitive compounds[6] in oven dried glassware (130°) under an atmosphere of oxygen- and moisture-free nitrogen. Nitrogen was dried by sequential passage through 50 mm x 1 m columns of Ridox[7] and Sicapent.[8]

THF first was distilled from KOH, followed by a second distillation from the purple ketal formed from potassium and benzophenone.[6c] Anhydrous Et_2O for aqueous extractions was used as received from Fisher Scientific, Inc. Dicyclopentadiene was freshly "cracked," distilled, and stored at -20° prior to use.[9] Sodium (Fisher Scientific, Inc.) was cleaned from its packing oil by three washings with THF, cut under THF, and used without further purification. Absolute ethanol was dried by distillation from sodium ethoxide, with diethylphthalate added (1 L EtOH, 7 g Na, 27.5 g DEP).[10] Sodium ethoxide was prepared *in situ* by dissolution of sodium in ~12 times its weight of freshly distilled absolute ethanol. Except where noted, all chemicals were purchased from Aldrich Chemical Co., Inc., checked by ^1H NMR and GC/MS for authenticity and purity, and distilled prior to use. ^1H NMR spectra were obtained at either 300 or 500 MHz on Varian Gemini 300 or VXR 500 spectrometers, respectively. Due to overlapping resonances, ring vinyl signal multiplicities were not resolved. $^{13}C\{^1H\}$ NMR spectra were measured at a field strength of 75 MHz on a Varian Gemini 300 spectrometer. Low resolution mass spectra were obtained on a Finnigan 4510 GC/MS spectrometer, high resolution mass spectra were obtained on an AEI MS 902 spectrometer, and GC/MS spectra were obtained on a HP 5880/5990A spectrometer. Reported boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.[11]

1-Chloro-3-ethoxypropane.- To 1-bromo-3-chloropropane (210 g, 1.34 mol) in a 2 L three-necked round bottomed flask equipped with a reflux condenser was added a solution of NaOEt (1.34 mol) in EtOH *via* a pressure equalizing funnel. The addition was carried out at ambient temperature in three equivalent portions, with a 30 min period of heating at boiling between each addition. After cooling to ambient temperature, the reaction mixture was quenched with H_2O (500 mL) and extracted with Et_2O (3 x 500 mL). The combined organic phase was washed with H_2O (3 x 500 mL) and dried ($MgSO_4$). After evaporation of the solvent, pure product (41 g, 25%) was obtained, bp. 128°, lit.[12] 125-128°. ^1H NMR and GC/MS data were consistent with the identity and purity of the compound.

1-Chloro-2-dimethylaminoethane.- In this modification of Burtner's[13] method, the compound was not isolated, but used immediately upon preparation in further synthesis. In a 2 L three necked round bottomed flask equipped with an overhead mechanical stirrer and a water cooled distillation condenser was placed $ClCH_2CH_2N(CH_3)_2{\cdot}HCl$ (98 g, 0.7 mol, used as received from Aldrich). To the tared receiving flask was added *ca.* 2 g of anhydrous Na_2CO_3 as a drying agent, and, to inhibit dimerization of the pure distillate, the receiving flask was cooled to *ca.* -20°. All at once, powdered NaOH (56 g, 1.4 mol) was added to the reaction flask and the mixture was stirred manually until the solid mass began to liquify (~5-10 min). Upon liquification, the mechanical stirrer was started and the distillation apparatus was attached to a water aspirator. The reaction flask was heated as needed to maintain distillation of pure monomeric product. In all cases, the product was used immediately in the preparation of **1d**, **2d**.

General Preparation of Alkylcyclopentadienes (1 and 2).- To a stirred suspension of sodium (11.5 g, 0.50 mol) in THF (250 mL) in a 500 mL three-necked round bottomed flask equipped with a water cooled condenser, serum septum, and pressure equalizing funnel, cyclopentadiene (HCp, 33 g, 0.50 mol) was added all at once *via* a syringe. The suspension was heated at boiling until all the sodium had disappeared and then cooled to ambient temperature.[14] A solution of $ClCH_2CH_2R$ (0.50 mol) in

THF (50 mL) was added dropwise to the stirred solution of NaCp. After the addition was complete, the reaction mixture was stirred at ambient temperature for 0.5 hr and subsequently heated at the boiling point for an additional 2 hrs. After cooling to ambient temperature, the reaction solution was diluted with Et_2O (250 mL) and extracted with H_2O (3 x 200 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated at ambient temperature on a rotary evaporator under water aspirator vacuum. The residue remaining in the flask was transferred to a fractional distillation apparatus fitted with a 0.75 m Vigreux column. Further purification by distillation yielded the regioisomeric mixtures of reaction products **1** and **2**. Although reduced pressure can be employed for all these distillations, it was only necessary for the purification of **1c**, **2c**. All compounds except for **1d** and **2d** appeared to be stable at the reported boiling points. Likewise, each compound appeared to be hydrolytically, oxidatively, photolytically, and thermally stable at ambient conditions for periods of at least several months.[11] However, after distillation, all products were stored at -20° to inhibit potential dimerization. **Table 1** presents a summary of isolated reaction yields, boiling points, and high resolution MS data, and **Table 2** contains a summary of ^1H NMR data. Further characterization data is given below. Compounds **1a**, **2a**, **1b**, and **2b** have been utilized previously, but full characterization data was not provided.[15]

TABLE 1 Yields, bps and HR Mass Spectra of **1** and **2**

Compound	Yield (%)	bp(°C)/(mm)	HR Mass Spectrum (Found)
1a, 2a	40	150/760	124.0888 (124.0897)
1b, 2b	50	160/760	138.1045 (138.1039)
1c, 2c	52	85/5	152.1201 (152.1206)
1d, 2d	45	170/760	—

***cyclo*-$C_5H_5CH_2CH_2CH_2OCH_2CH_3$ (1c, 2c):** $^{13}C\{^1H\}$ NMR in $CDCl_3$ [δ, down field value taken as positive, relative to $Si(CH_3)_4$ = 0.0 PPM, referenced to solvent resonance at 77.0 PPM; (assignment of resonance)]: 14.94 (CH_3); 26.14, 26.96, 28.67, 29.51 (α and β CH_2); 41.03, 43.08 (O-CH_2CH_3); 66.00, 77.10 (CH_2CH_2-O); 126.13, 126.57, 130.68, 132.53, 133.85, 134.86, 146.79, 149.45 (C_5H_5 ring). Low resolution MS [m/e (relative intensity)]: 79 (100), 90 (95), 78 (53), 77 (52), 76 (39), 105 (26), 104(19), 151 (15, M^+).

***cyclo*-$C_5H_5CH_2CH_2N(CH_3)_2$ (1d, 2d):** $^{13}C\{^1H\}$ NMR in $CDCl_3$ [δ, down field value taken as positive, relative to $Si(CH_3)_4$ = 0.0 PPM, referenced to solvent resonance at 77.0 PPM; (assignment of resonance)]: 27.90, 28.68 (α CH_2); 40.94, 43.05, 45.11 (CH_3); 58.77, 59.47 (CH_2-N); 126.86, 126.88, 130.70, 132.38, 133.74, 134.56, 144.95, 147.37 (C_5H_5 ring). Low resolution MS [m/e (relative intensity)]: 58 (100), 137 (3, M^+, second most intense peak observed in spectrum).

Anal.[11] Calcd for $C_9H_{15}N$: C, 78.78; H, 11.01. Found: C, 78.16; H, 10.77

TABLE 2. ^{1}H NMR Data for Compounds 1 and 2[a]

Cmpd	ring CH_2	ring vinyl	α-CH_2	β-CH_2	γ-CH_2	CH_3[b]	CH_2[c]
1a, 2a	2.86, 2.90 [4; 2H on **a** (C5) and 2H on **b** (C3)]	6.03, 6.17, 6.22 [3]; 6.34, 6.40 [3]	2.61($^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.7 Hz), 2.63 ($^3J_{HH}$ = 6.6 Hz; $^4J_{HH}$ = 1.1 Hz) [4]	3.48, 3.51 [4]	N/A	3.29, 3.30 [6]	N/A
1b, 2b	2.89, 2.91 [4; 2H on **a** (C5) and 2H on **b** (C3)]	6.04, 6.19, 6.24 [3]; 6.38, 6.42 [3]	2.63 ($^3J_{HH}$ = 7.1 Hz; $^4J_{HH}$ = 1.6 Hz), 2.66 ($^3J_{HH}$ = 6.6 Hz; $^4J_{HH}$ = 1.6 Hz) [4]	3.52, 3.57 [4]	N/A	1.171 ($^3J_{HH}$ = 7.1 Hz), 1.174 ($^3J_{HH}$ = 7.1 Hz) [6]	3.45, 3.48 [4]
1c, 2c[d]	2.85, 2.88 [4; 2H on **a** (C5) and 2H on **b** (C3)]	6.05, 6.17, 6.25 [3]; 6.40, 6.45 [3]	2.43, ($^3J_{HH}$ = 7.8 Hz; $^4J_{HH}$ = 1.4 Hz), 2.48 ($^3J_{HH}$ = 7.8 Hz; $^4J_{HH}$ = 1.4 Hz) [4]	1.83, 1.84 [4; t of t]	3.42, 3.44 [8; CH_2-O-CH_2 coincidental overlap]	1.15 ($^3J_{HH}$ = 7.1 Hz [6]	3.42, 3.44 [8; CH_2-O-CH_2 coincidental overlap]
1d, 2d	2.85, 2.90 [2; 2H on **a** (C5) and 2H on **b** (C3)]	5.99, 6.36, 6.37, 6.39, 6.40 [3]	2.36 - 2.56 (4; br m, 2.46 maxima)	2.36 - 2.56 (4; br m, 2.46 maxima)	N/A	2.21, 2.22 [6]	N/A

a) δ from TMS and referenced from residual $CHCl_3$ at δ 7.24 at 300 MHz except as otherwise noted, integrated areas in brackets. b) On or α- to heteroatom. c) On heteroatom. d) At 500 MHz.

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11. Amine substituted compounds **1d**, **2d** were stable at ambient conditions for only brief time periods. Therefore, significant decomposition occurred during attempts to obtain pure samples for elemental analysis. This demonstrated lack of stability in no way hindered us in the use of these compounds in further synthetic reactions. So long as the subsequent reactions were performed within a few hours of distillation, little decomposition was evidenced.

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SYNTHESIS OF MODELS RELATED TO TASPINE

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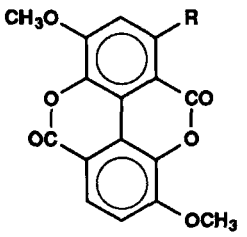
Taspine (**1a**)[1] is an alkaloid with an unusual diphenylic skeleton, whose synthesis has not been yet reported. A previous note[2] described the synthesis of a model compound **1b**, which was not suitable for further transformation into taspine, owing to its insolubility in most common solvents. Our efforts torward the total synthesis of **1a**, led us to develop a similar strategy for the synthesis of another model compound **1c**, which has a direct structural relationship to taspine. Furthermore, we expected that **1c** would be more soluble than **1b**, owing to the presence of the propionic acid chain, which could be converted into the 2-(N-dimethylamino)ethyl group of taspine **1a**, by a previously discovered modification of the Curtius reaction that gave good yields when applied to dihydroferulic acid.[3]



1

a R = $(CH_2)_2NMe_2$
b R = Me
c R = $(CH_2)_2CO_2H$
d R = H

By analogy to the synthesis of the dilactone **1b** , we initially synthesized the diphenylic dialdehyde **3** (41% yield), by Ullmann coupling[4] of an excess of the less reactive bromoaldehyde **2c**[2] with the bromoaldehyde **2b**;[5] however, **3** could not be transformed into the dilactone **1c** due to the resistance of the formyl groups to oxidation, presumably for steric reasons. We thus oxidized the bromoaldehyde **2b** with Jones reagent[6] under controlled conditions to give acid **4a**, which was treated with diazomethane to afford ester **4b**. The Ullmann reaction was performed in boiling DMF with an excess of bromoester **5**,[2] to avoid losses of component **4b** by self-condensation. This lower temperature of about 70°, as compared to previous conditions,[2] gives better yields. The asymmetric diphenylic diester **6a** was isolated in 52% yield, along with the previously described[2] dimer of **5**. Hydrogenolysis of **6a** gave, in quantitative yield, debenzylated **6b** which was hydrolyzed in alkaline medium; acid **6c**, which was not isolated, was converted in high yield into the dilactone **1c** by the