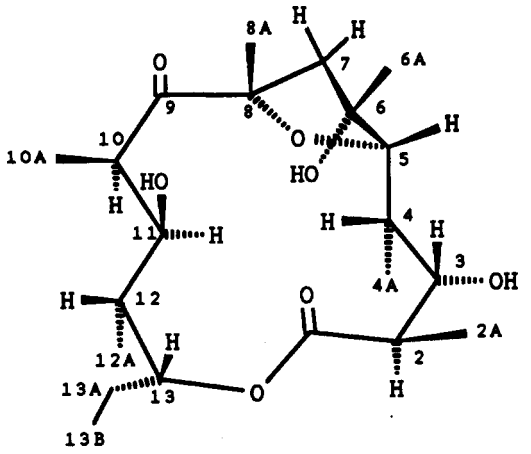

Figure 2. Proposed conformation of 6.

heterocorrelated spectroscopy. The ^1H NOE values were determined by using the monodimensional difference spectroscopy technique. Typically 5–7 experiments were performed with a selective irradiation of different protons and then subtracted from a control spectrum (off resonance irradiation). IR spectra were recorded on a Perkin-Elmer 467 spectrometer. Ultraviolet (UV) spectra were measured in methanol, using a Jasco UVIDEC-510 spectrophotometer. Optical rotations were determined at 20 °C in methanol solutions with a Jasco DIP-181 polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ 70 spectrometer in the CI mode, using isobutane as reagent gas: source temperature 150 °C, isobutane pressure 4500 mTorr. HPLC analyses were carried out on a Jasco Twincle HPLC, equipped a UV detector (210 nm) and a chromatographic data system under the following conditions: reverse phase C-18 (2.5 × 100) Jasco column (7-μm particles); mobile phase acetonitrile–0.01 M phosphate buffer pH 7.0 (1:1); flow rate 1.5 mL/min at 40 °C. Thin-layer chromatography (TLC) was performed with aluminum-backed Merck silica gel 60 F254 plates. Melting points were determined on a Thomas hot-stage apparatus and are uncorrected.

(8*S*)-8-Bromo-9-deoxo-5,6-dideoxy-5,9:6,9-diepoxyerythronolide B (3). (A) A solution of erythronolide B (2.0 g, 5.2 mmol) in glacial acetic acid (30 mL) was stirred at room temperature for 1 h. *N*-Bromoacetamide (0.80 g) was slowly added. After being stirred at room temperature for 30 min, water was added and **3** precipitated as a pure white solid (2.0 g, 82%): mp 111 °C dec; after crystallization from hexane mp 115 °C dec; $[\alpha]_D$ +34.7°; UV (EtOH) λ_{max} 202 (ϵ 716); IR (KBr) 3535, 3445, 1732, 1170, 1050, 920 cm^{-1}; LRCIMS *m/z* 465–463 $(M + 1)^+$ (65), 447–445 (15), 401 (27), 384 (60), 383 (100), 365 (87), 347 (32), 285 (17), 205 (39). Anal. Calcd for $C_{21}H_{35}BrO_6$: C, 54.43; H, 7.61; Br, 17.24. Found: C, 54.21; H, 7.65; Br, 17.16.

(B) *N*-Bromoacetamide (0.4 g) was added to a solution of 8,9-didehydro-9-deoxo-6-deoxy-6,9-epoxyerythronolide B (**2**) (1.0 g, 2.5 mmol) in various solvents (15 mL) and the mixture was stirred for 30 min. Water was added and compound **3** precipitated. Solvent: (i) glacial acetic acid (1.15 g, 96%), mp 111 °C dec; IR (Nujol) 3560, 3525, 1720 cm^{-1}; (ii) chloroform/water (1.0 g, 83.4%), mp 111 °C dec; IR (Nujol) 3525, 3445, 1730 cm^{-1}; (iii) methanol (0.72 g, 60%), mp 115 °C dec; IR (Nujol) 3560, 3525, 3445, 1730, 1720 cm^{-1}.

5-Deoxy-5,8-epoxy-8-*epi*-erythronolide B (6). A solution of bromoerythronolide spiroacetal **3** (0.5 g) in acetonitrile (10 mL) was stirred with silver fluoride (or silver difluoride) (0.2 g) for 1 h at room temperature. The mixture was filtered and a solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate and the organic layer was dried, filtered, and evaporated. The crude product was purified by crystallization from toluene (0.39 g, 93%): mp 240 °C; $[\alpha]_D$ −72.8°; UV (EtOH) λ_{max} 290 nm (ϵ 71); IR (KBr) 3480, 3380, 3320, 3240, 1725, 1690, 1455, 1380, 1335, 1175, 1130 cm^{-1}; ^1H NMR (pyridine) δ 5.78 (1 H, dd, H-13, J(13,14) = 5.0 Hz, J(13,14′) = 9.0 Hz), 4.88 (2 H, d, H-3 and H-11, J(2,3) = J(11,12) = 9.6 Hz), 4.03 (1 H, d, H-5, J(4,5) = 8.4 Hz), 3.90 (1 H, q, H-10, J(10,Me) = 6.9 Hz), 3.00 (1 H, d, H-7a, J(7a,7b) = 12.3), 1.90 (1 H, d, H-7b)); LRCIMS *m/z* 401 $(M + 1)^+$ (45), 383 (100), 365 (10), 285 (10), 245 (10). Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.97; H, 9.06. Found C, 62.85; H 8.91.

9-Deoxo-5,6-dideoxy-5,8:6,9-diepoxy-9-fluoro-8-*epi*-erythronolide B (5). A solution of bromoerythronolide spiroacetal **3** (0.5 g) in anhydrous acetonitrile (10 mL) was stirred with silver fluoride (or silver difluoride) (0.2 g) at room temperature under N_2 until the TLC analyses showed the disappearance of the starting material. The mixture was filtered and evaporated. Anal. (Crude product). Calcd for $C_{21}H_{35}FO_6$: C, 62.67; H, 8.77; F, 4.72. Found: C, 62.00; H, 8.60; F, 4.93. TLC analysis of the reaction solution, immediately at end of the reaction, showed **5** as the main product with traces of **6**; after 3 h, **6** was the only product present in solution. Analytical and spectroscopical data are not given because it was not possible to purify the product.

X-ray crystallographic analysis of 3: $C_{21}O_6H_{35}Br$, FW = 463.4, orthorhombic, space group $P2_12_12_1$, a = 23.985 (7), b = 11.202 (4), and c = 8.503 (3) Å, V = 2285 (1) Å^3, Z = 4, ρ = 1.35 g cm^{-3}, μ = 18.1 cm^{-1}, F(000) = 976, 0.35 × 0.15 × 0.03 mm, colorless, transparent crystal, Philips PW 1100 diffractometer, λ(Mo Kα) = 0.71063 Å, graphite monochromated, ambient temperature, lattice parameters from least-squares refinement of 16 reflections with $2\theta \geq 13°$, standard reflections (102, 102) measured every 90 min to check crystal stability and experimental conditions, no significant variations detected; 2037 unique reflections $(h, -k, l)$ with $5° \leq 2\theta \leq 48°$ were collected, 831 with $I \geq 2.5\sigma(I)$ being used for all analysis. $\theta/2\theta$ scans, constant scan speed 0.04° s^{-1}, two background counts of 7 s at each side of the peak and values averaged. Lorentz polarization but no absorption correction was applied. The position of the Br atom was determined from a Patterson synthesis, while other atoms were located by standard Fourier methods. The refinement was carried out by blocked-full-matrix least-squares, using SHELX76[14] using an optimized weighting scheme in the final cycles. Given the relative paucity of data, all atoms, except for the bromine, were refined isotropically. Hydrogen atom positions were refined in the riding mode with a common isotropic temperature factor, after inclusion at calculated positions, with the exception of hydroxyl hydrogens, which were located from Fourier difference maps. Final R, R_w, and goodness of fit values were 0.0627, 0.0485, and 1.86, respectively, while the maximum and minimum in the final difference map were 0.47 and −0.45 e Å^{-3}. The absolute configuration was determined by comparing the R values of the two enantiomeric structures at an early stage of the refinement, yielding R values of 0.102 and 0.094. The enantiomer with higher R value may be rejected at a high significance level.

Acknowledgment. We thank Professor F. Minisci for helpful discussion. This work was carried out in the frame of "Programma Nazionale di Ricerca per la Chimica" and committed by MURST to Tecnofarmaci.

Supplementary Material Available: Atomic coordinates, equivalent isotropic displacement parameters, bond lengths, and bond angles from the X-ray crystallographic analyses of **3** (5 pages). Ordering information is given on any current masthead page.

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Trisannelated Benzene Synthesis by Zirconium Halide Catalyzed Cyclodehydration of Cycloalkanones

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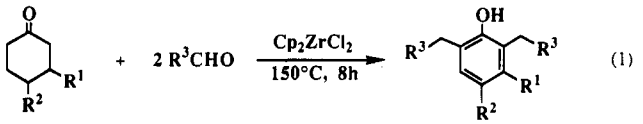
Received August 9, 1990

The physical and chemical properties of trisannelated benzene derivatives, such as trindan (**1**) and dodecahydrotriphenylene (**2**), and its analogues have been extensively studied.[1] For example, the trindenyl trianion

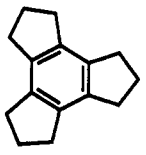
derived from 1 is a useful di- or trinucleating ligand,[2] and 2 is utilized as a η^6-aryl ligand in an (arene)tricarbonylmanganese cation complex.[3] Compounds 1 and 2 were first prepared as minor products of the acid-catalyzed condensation of cyclopentanone (5)[4] and cyclohexanone (6),[5] respectively. Although several methods have been reported for the preparation of 2,[6] there have been very few studies so far on the preparation of 1.[4,7]

In a previous paper, we reported that bis(η^5-cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) catalyzes the aldol condensation–aromatization of cyclohexanones and aldehydes to afford 2,6-dialkylphenols in fair to good yields (eq 1).[8] We have now found that this method may be

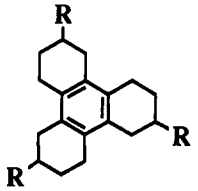


(1)

extended to a facile one-step preparation of trisannelated benzene derivatives 1–4 through the cyclodehydration of the corresponding cycloalkanones 5–9.



1



2 : R = H
3 : R = Me
4 : R = t-Bu

The potential of several group IVa metal halides and Lewis acids for the condensation of cyclohexanone (6) was examined (Table I). Reactions were carried out at 150–200 °C for 8 h in the presence of catalyst without solvent.

Among the catalysts examined, only group IVa metal halides were efficient for the cyclodehydration of 6 to 2. In particular, zirconium chlorides were found to be effective catalysts, which show a high capability to condense 6. In the condensation–aromatization of 6 and aldehydes into 2,6-dialkylphenols, Cp_2ZrCl_2 was more efficient than $ZrCl_4$ (eq 1),[8] but in the present reactions Cp_2ZrCl_2 was inferior to $ZrCl_4$. Although zirconium analogue $HfCl_4$ indicated relatively high activity for the cyclodehydration of 6 to 2, $TiCl_4$ and Cp_2TiCl_2 afforded only trace amounts of 2. Typical Lewis acids, such as $AlCl_3$, $FeCl_3$, $SnCl_4$, and ZnI_2, were found to be poor catalysts. It has been reported that $ZnCl_2$ catalyzes the cyclodehydration of 6 to 2 in 3% yield.[6b]

The catalytic activity of several zirconium compounds was examined under varying conditions. By the use of 0.02 equiv of $ZrCl_4$, the yield of 2 was lowered to 57% (run 5). Unlike $ZrCl_4$, the Cp_2ZrCl_2-catalyzed reaction showed higher yield at 150 °C than 200 °C (run 2). It is interesting to note that $Zr(OBu)_4$ did not catalyze the condensation of 6, but the $Zr(OBu)_4$–HCl system[9] promoted the cyclodehydration to afford 2 in 30% yield. However, the $Zr(OBu)_4$–H_2SO_4 system[9] and $Zr(SO_4)_2$ failed to catalyze the cyclodehydration (runs 9 and 10). The best result was obtained when 6 was allowed to react under the influence of $ZrCl_4$ (0.04 equiv) at 200 °C for 8 h (run 4). After recrystallyzation from chloroform, 2 was isolated as a white precipitate in 70% yield.

On the basis of these results, several cycloalkanones were allowed to react in the presence of a catalytic amount (0.04 equiv) of $ZrCl_4$ or Cp_2ZrCl_2 (Table II).

Cyclopentanone (5) underwent cyclotrimerization under similar conditions to give trindan (1) in fair yield (40%). Mayer[7] has prepared 1 in 18–20% yield by self-condensation of 5 catalyzed by hydrochloric acid.

The influence of alkyl substituents on the cyclohexanone ring on the trisannelation was studied. The regioselectivity

Table I. Cyclodehydration of Cyclohexanone (6) to Dodecahydorotriphenylene (2) by Various Metal Halides[a]

run	catalyst	temp, °C	conv,[b] %	yield,[c] %
1	Cp_2ZrCl_2	150	86	41
2	Cp_2ZrCl_2	200	92	29
3	$ZrCl_4$	150	92	61
4	$ZrCl_4$	200	96	70
5[d]	$ZrCl_4$	200	87	57
6	$ZrOCl_2$	150	76	12
7	$Zr(OBu)_4$	200	34	
8	$Zr(OBu)_4$–HCl[e]	200	70	31
9	$Zr(OBu)_4$–H_2SO_4[f]	200	56	trace
10	$Zr(SO_4)_2$	200	55	trace
11	Cp_2TiCl_2	150	76	trace
12	$TiCl_4$	150	>98	trace
13	$HfCl_4$	150	92	57
14	$AlCl_3$	150	79	
15	$FeCl_3$	150	76	
16	ZnI_2	150	54	
17	$SnCl_4$	150	76	

[a] 6 (20 mmol) was allowed to react in the presence of catalyst (0.8 mmol, 0.04 equiv) for 8 h. [b] Determined by GLC. [c] Isolated yield. [d] $ZrCl_4$ (0.4 mmol) was used. [e] 35% HCl (0.28 mL, 3.2 mmol) was added. [f] 95% H_2SO_4 (0.093 mL, 1.6 mmol) was added.

Table II. Preparation of Trisannelated Benzene Derivatives from Cycloalkanones Catalyzed by Zirconium Chlorides[a]

substrate	catalyst	temp, °C	conv,[b] %	product no.	product yield[c] %
cyclopentanone (5)	$ZrCl_4$	150	>99	1	40
	Cp_2ZrCl_2	150	95	1	27
cyclohexanone (6)	$ZrCl_4$	200	96	2	70
	Cp_2ZrCl_2	150	86	2	41
4-methylcyclohexanone (7)	$ZrCl_4$	200	95	3	60 (6:4)[d]
	Cp_2ZrCl_2	150	90	3	35
4-*tert*-butylcyclohexanone (8)	$ZrCl_4$	150	81	4	36
	Cp_2ZrCl_2	150	75	4	41 (6:4)[e]
3-methylcyclohexanone (9)	$ZrCl_4$	150	75	3	41 (1:1)[d]
	Cp_2ZrCl_2	150	68	3	35
2-methylcyclohexanone	$ZrCl_4$	200	45		
	Cp_2ZrCl_2	150	20		

[a] Cyclohexanone (20 mmol) was allowed to react under the influence of zirconium catalyst (0.8 mmol, 0.04 equiv) for 8 h. [b] Determined by GLC. [c] Isolated yield. Remainders involve bis and tris aldol condensation products. [d] Ratio of 3a to 3b. [e] Ratio of 4a to 4b.

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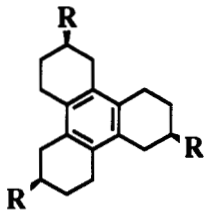
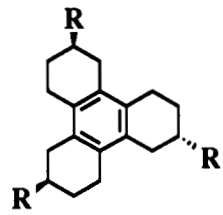
(9) The reactions were carried out by adding 35% HCl (0.28 mL, 3.2 mmol) or 95% H_2SO_4 (0.03 mL, 1.6 mmol) to $Zr(OBu)_4$ (0.8 mmol), respectively.

of the trisannelation was found to depend markedly on the position of the alkyl substituent on the cyclohexanone ring.

The reaction of 4-methylcyclohexanone (7) catalyzed by $ZrCl_4$ at 200 °C afforded the corresponding trisannelated products **3a** and **3b** in a ratio of ~6:4. Because of the



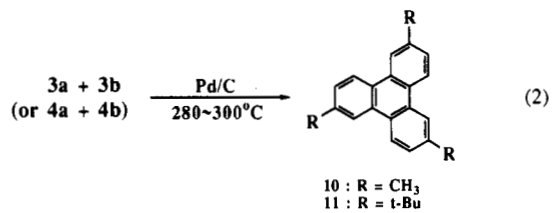
3a : R = CH_3
4a : R = t-Bu



3b : R = CH_3
4b : R = t-Bu

similarity of the physical properties of these isomers, it was difficult to separate them. The major isomer, **3a**, showed a seven-line ^{13}C NMR spectrum, while the minor compound, **3b**, indicated many carbon signals. The former spectrum is in good agreement with the structure of dodecahydro-2,6,10-trimethyltriphenylene (**3a**) possessing C_3 symmetry. That the latter compound, **3b**, possesses an unsymmetrical structure is evident from its ^{13}C NMR spectrum. When the orientation of one methyl substituent of **3a** is different from the other two, the C_3 symmetry of **3a** is lost and the compound may show 21 carbon signals in the ^{13}C NMR spectrum. Furthermore, the formation of regioisomers from **7** is unlikely if the cyclodehydration pathway illustrated in Scheme I is correct. Therefore, **3b** was considered to be a stereoisomer of **3a**, differing in the orientation of a methyl substituent on the cyclohexane ring.

If **3a** and **3b** are stereoisomeric with each other, the aromatization of these compounds by dehydrogenation will produce the same dehydrogenated product, 2,6,10-trimethyltriphenylene (**10**). As expected, the dehydrogenation of a mixture of **3a** and **3b** on Pd/C led to the sole product, which is assigned structure **10** (eq 2).



10 : R = CH_3
11 : R = t-Bu

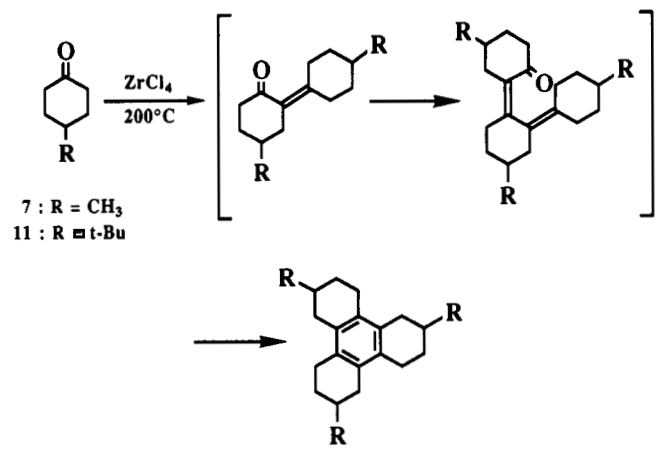
(2)

It is noteworthy that the trisannelation of 3-methylcyclohexanone (**9**) occurred selectively at the sterically less hindered 6-position to give the same trisannelated products, **3a** and **3b**, as that of **7**. From the kinetic and thermodynamic points of view, it is probable that the condensation at the 6-position of **9** is preferable to that at the 2-position. Consequently, the regioselective formation of **3** from **9** presumably occurs via a sequence involving double aldol condensation at the 6-position and cyclodehydration of the resulting enone (Scheme II). However, from the reaction of 2-methylcyclohexanone, no trisannelated product could be obtained.

In a similar manner as **7**, 4-*tert*-butylcyclohexanone (**8**) gave a stereoisomeric mixture of dodecahydro-2,6,10-tri-*tert*-butyltriphenylenes (**4a** and **4b**) in a ratio of 6:4. The dehydrogenation of **4a** and **4b** afforded only 2,6,10-tri-*tert*-butyltriphenylene (**11**) having C_3 symmetry.

In conclusion, zirconium chlorides Cp_2ZrCl_2 and $ZrCl_4$ were found to be efficient catalysts for the cyclodehydration of cycloalkanones to the corresponding tris-

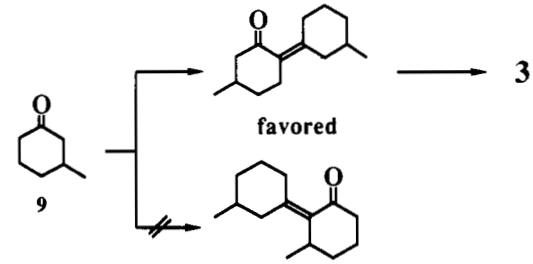
Scheme I



7 : R = CH_3
11 : R = t-Bu

3 : R = CH_3
4 : R = t-Bu

Scheme II



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annelated benzenes, which previously were difficult to prepare in satisfactory yield by a one-step reaction. This method provides a simple way to prepare **1** and **2** as well as triphenylene derivatives **3** and **4**.

Experimental Section

Melting points are uncorrected. GLC analyses were carried out on a Shimadzu capillary column, HiCap CBP1-M25-25. Column chromatography was performed with Wako gel 60 (230–400 mesh).

Representative Procedure for Trisannelation of Cycloalkanones. Dodecahydrotriphenylene (2). Cyclohexanone (20 mmol, 1.96 g) and $ZrCl_4$ (0.8 mmol, 18.6 mg) were poured in an 50-mL autoclave, and the mixture was heated with shaking at 200 °C for 8 h. The resulting product was dissolved with $CHCl_3$, and the catalyst was removed by filtration. The filtrate was concentrated by evaporation, and the remaining solid was recrystallized from $CHCl_3$–hexane (7:3, v/v) to give dodecahydrotriphenylene (**2**) as a white precipitate (1.12 g, 70%). Dodecahydrotriphenylene (**2**): mp 230–231 °C (lit.[6b] mp 230 °C); IR (KBr) 2926, 2851, 1450, 1311, 1253 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 2.5 (s, 12 H), 1.73 (s, 12 H); ^{13}C NMR ($Me_4Si/CDCl_3$) δ 132.4 (s), 26.9 (t), 23.1 (t).

Arene products **3** and **4** were obtained by the same workup as above, while **1** was isolated by column chromatography on silica gel eluting with hexane. Trindan (**1**): 0.53 g, 40%; mp 96–97 °C (lit.[7] mp 97.5–98 °C); IR (KBr) 2837, 1448, 1424, 1300, 1275 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 3.2–2.5 (t, J = 7.3 Hz, 12 H), 2.4–1.9 (m, 6 H); ^{13}C NMR ($Me_4Si/CDCl_3$) δ 137.6 (s), 31.2 (t), 25.5 (t). Dodecahydro-2,6,10-trimethyltriphenylenes (**3a** and **3b**): 113 mg, 60%; IR (KBr) 2947, 2912, 2867, 1455, 1433, 1371 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 2.7–2.4 (m, 3 H), 2.0–1.6 (m, 18 H), 1.1 (m, 9 H); ^{13}C NMR ($Me_4Si/CDCl_3$) (**3a**) δ 132.5 (s), 132.1 (s), 36.1 (t), 31.4 (t), 29.1 (t), 27.5 (d), 22.6 (q), (**3b**) δ 132.5 (s), 132.2 (s), 132.0 (s), 35.9 (t), 35.4 (t), 35.1 (t), 35.1 (t), 31.3 (t), 30.8 (t), 29.0 (t), 28.8 (t), 28.5 (t), 27.2 (d), 26.6 (d), 26.0 (d), 22.4 (q), 22.3 (q), 21.8 (q). Dodecahydro-2,6,10-tri-*tert*-butyltriphenylenes (**4a** and **4b**): 111 mg, 41%; IR (KBr) 2961, 2867, 1477, 1435, 1393, 1365, 1247, 1232 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 2.9–2.5 (m, 3 H), 1.55–1.35

(m, 18 H), 0.99 (s, 27 H); ^{13}C NMR ($Me_4Si/CDCl_3$) (**4a**) δ 132.7 (s), 132.5 (s), 44.5 (d), 32.4 (s), 28.7 (t), 28.4 (t), 27.2 (q), 24.4 (t), (**4b**) δ 133.1 (s), 132.9 (s), 132.8 (s), 132.7 (s), 132.6 (s), 132.5 (s), 132.3 (s), 44.5 (d), 44.4 (d), 32.5 (s), 32.4 (s), 28.8 (t), 28.7 (t), 28.4 (t), 28.1 (t), 27.9 (t), 27.7 (t), 27.7 (q), 27.3 (q), 27.2 (q), 24.4 (t), 24.3 (t), 24.2 (t).

Dehydrogenation of Dodecahydro-2,6,10-trimethyltriphenylenes (3a and 3b). The mixture of **3a** and **3b** (0.38 mmol, 108 mg) was heated at 280-300 °C with 5% Pd/C (200 mg) in a 50-mL autoclave for 10 h. The reaction product was extracted with $CHCl_3$. Evaporation of the solvent gave almost pure 2,6,10-trimethyltriphenylene (**10**) (98 mg, 95%) without further purification. The dehydrogenation of **4a** and **4b** was carried out by the same method as above. 2,6,10-Trimethyltriphenylene (**10**): mp 181-182 °C; IR (KBr) 3025, 2917, 2852, 1615, 1503, 1408, 1372, 1262, 816, 765, 593 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 8.33 (d, J = 8.4 Hz, 3 H), 8.22 (s, 3 H), 7.23 (d, J = 6.6 Hz, 3 H), 2.43 (s, 9 H); ^{13}C NMR ($Me_4Si/CDCl_3$) δ 136.5 (s), 129.9 (s), 128.0 (d), 126.9 (s), 123.1 (d), 123.0 (d), 21.8 (q). Anal. Calcd for $C_{21}H_{18}$: H, 6.71; C, 93.29. Found: H, 6.57, C, 93.18. 2,6,10-Tri-*tert*-butyltriphenylene (**11**): 135 mg, 90%; mp 293-294 °C; IR (KBr) 2963, 2902, 2866, 1618, 1502, 1479, 1458, 1409, 1362, 1264, 824, 652 cm^{-1}; ^1H NMR ($Me_4Si/CDCl_3$) δ 8.6 (s, 3 H), 8.6 (d, J = 11.7 Hz, 3 H), 7.70 (d, J = 8.4 Hz, 3 H), 1.50 (s, 27 H); ^{13}C NMR ($Me_4Si/CDCl_3$) δ 149.6 (s), 129.5 (s), 127.5 (s), 124.6 (d), 122.9 (d), 119.1 (d), 35.0 (s), 31.5 (q). Anal. Calcd for $C_{30}H_{36}$: H, 9.15, C, 90.85. Found: H, 9.21, C, 90.78.

Highly Regioselective Functionalization of 2,3-Dialkyl Substituents on Indoles

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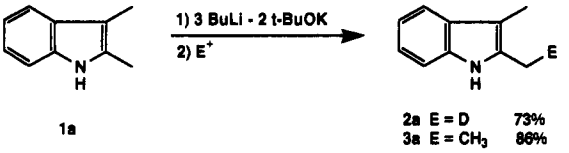
Received July 13, 1990

Direct functionalization of the side chains of heteroaromatic nuclei continues to be a significant challenge for the construction of complex alkaloids.[1] The α-metalation of alkyl substituents is one of the most attractive routes for this modification.[2] Although the indole and pyrrole rings are widely found in bioactive compounds, little attention has been paid to the deprotonation of the alkyl side chains on these π-excessive heteroaromatics. During the course of our study of the stabilization of cross-conjugated [6 electrons/4 p orbitals] system,[3,4] we have succeeded in generating a C,N-dianion of 2-methylindole by a particular sequence of base treatments and in introducing some functional groups into the side chains.[5,6] The successful transformation might be due to the stability of the benzene ring and the cross [6e/4p] conjugation in the dianion intermediate.[6] This assumption led us to explore the deprotonation of 2,3-dialkylated indoles. The reaction would predominantly occur at the 2-alkyl side chain.[3] Here we report that the direct metalation of polysubstituted indoles proceed in a highly regioselective manner.

Our first choice for the reaction was 2,3-dimethylindole (**1a**). Treatment of **1a** with butyllithium (3 equiv) followed by addition of potassium *tert*-butoxide (2 equiv)[15] in ether at ambient temperature afforded a bright yellow suspension of the dianion. Quenching by methanol-d_1 (10 equiv) gave 2-(deuteriomethyl)-3-methylindole (**2a**) in 73% yield. The ^{13}C NMR spectra of the N-methylated product showed that the reaction proceeded only at the α-position of 2-methyl group.



The methylation with methyl halides occurred in a similar manner (Table I). A sole product, 2-ethyl-3-methylindole (**3a**) was obtained. The regioselectivity was determined by the differential NOE experiment. Interestingly, methyl bromide was found to be superior as an electrophile to methyl iodide. The usual S_N2 reactivity of alkyl halides is R-I > R-Br > R-Cl > R-F.[7]

Deprotonation of 1,2,3,4-tetrahydrocarbazole (**1c**)[8] also proceeded exclusively at the 1-position (runs 7, 8). No ortho-metalation on the benzene ring occurred. The results form a striking contrast to that observed by Katritzky et al. when the protecting groups of chelating capability were attached to the N atom. Their procedures failed in case of the carboxylate group[9] and led to the ortho-metalation in case of the 1-pyrrolidinomethyl group.[10]

Herein a novel method for the highly regioselective deprotonation of the indole alkyl substituents has been established by the particular sequence of base treatments. This success may be due to the aromatic stabilization of cross [6e/4p] conjugated systems. We are presently pursuing further application revolving around this methodology.

Experimental Section

General. All experiments were performed under Ar atmosphere. Diethyl ether as solvent was distilled from sodium benzophenone ketyl. The reagents are commercial products and used without further purification, unless literature sources or details for the preparation are given. 1,2,3,4-Tetrahydrocyclopent[*b*]-indole (**1d**) and the authentic samples of 2-ethyl-3-methylindole (**3a**) and 1-deuterio-1,2,3,4-tetrahydrocarbazole (**2c**) were prepared in the analogous fashion of 1,2,3,4-tetrahydrocarbazole.[8] Thin-layer chromatography (TLC) analyses were performed with Merck 5715 precoated plate. NMR spectra of ^1H nuclei at 270 MHz and of ^{13}C nuclei at 60 MHz were recorded by a JEOL GX-270 spectrometer. Melting points were measured by a Yanagimoto MP-J3 and are uncorrected. IR spectra were recorded by a JASCO A-100 or a Perkin-Elmer 1640SF spectrometer. Mass spectra (MS) were obtained on a Shimadzu GCMS 9020-DF instrument. Yields of the deuterized products were obtained by the decrease of ^1H NMR integration. The elemental analysis was performed at the

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