molar shift $\Delta\nu_m^B$ = 169 Hz/mol, which after correction for the naphthalene ASIS was 162 Hz/mol (2.03 ppm/mol). Similarly, the ASIS-free $\Delta\nu_m^a$ was found to be equal to 178 Hz/mol (2.23 ppm/mol).

Registry No. $Li^+C_{10}H_8^{-\cdot}$, 7308-67-0; Ph_3CCOPh, 466-37-5; $Li^+(Ph_3CCOPh)^{-\cdot}$, 83802-04-4; $(Ph_3CCOPh)^{2-}2K^+$, 83802-05-5; THF, 109-99-9; fluorenone, 486-25-9; anthraquinone, 84-65-1.

Direct Geminal Dialkylation of Ketones Using Organotitanium Reagents. A Simple Entry into Synthetic Tetrahydrocannabinoids

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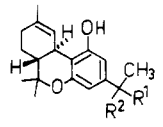
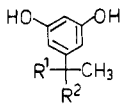
Replacing the *n*-pentyl side chain of natural or synthetic tetrahydrocannabinoids[1] by more lipophilic *tert*-alkyl groups has a profound influence on the pharmacological properties.[1-4] Many syntheses of natural or synthetic Δ^1-tetrahydrocannabinoids (e.g., **1**) as well as their $\Delta^{1(6)}$



1



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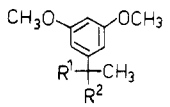

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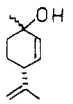


4

CH_3TiCl_3

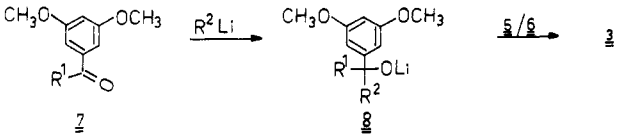
5

$(CH_3)_2TiCl_2$

6

isomers make use of acid-mediated condensation of 5-substituted resorcinols (e.g., **2**) with such terpenes as *p*-mentha-2,8-dien-1-ol (**4**).[1,2] Since the meta substitution pattern in **2** prohibits simple Friedel-Crafts *tert*-alkylation, several multistep procedures have been developed, most of them leading to dimethyl derivatives **3** which are then converted into **2**.[1,2,4] We describe a new and variable way to synthesize compounds **3** using the titanium reagents[5] **5** and **6**.

Our strategy is based upon the formal replacement of the carbonyl oxygen atom in ketones **7** by two alkyl groups. Such geminal dialkylation has been accomplished in other systems by a simple three-step sequence:[6] (1) Grignard addition, (2) formation of the tertiary alkyl chloride, and (3) methylation by using **5** or **6**. Unfortunately, in the present case the corresponding cumyl chlorides are rather sensitive. We have therefore developed a one-pot procedure. Addition of the alkyllithium to **7** in hexane followed



7 **8**

*by the reaction of the lithium alcoholates **8** with a 1:1 mixture of **5** and **6** in methylene chloride (method A) results in smooth formation of **3*** (Table I). In spite of the fact that this unusual C-C bond-forming reaction probably involves intermediate carbocations, position specificity pertains. Undesired Wagner-Meerwein rearrangements or retro-Friedel-Crafts reactions are not observed. If the amount of methylating reagent is reduced, the yields of **3** are lower. In order to introduce two new methyl groups, direct geminal dimethylation[7] of **7** by employing **6** is the method of choice (method B, Table I).

Demethylation of **3** to form **2** can be accomplished by using acids or trimethylsilyl iodide.[2,4] Condensation of resorcinols of the type **2** has been carried out with *p*-toluenesulfonic acid to form the $\Delta^{1(6)}$ isomer of **1**, which can be easily isomerized to **1**.[2]

Thus, the present methodology for the construction of quarternary carbon atoms represents a variable entry into synthetic tetrahydrocannabinoids of the type **1**.

Table I. Direct Geminal Dialkylation of Ketones 7

R^1	R^2	method	isolated 3 (% yield)
CH_3	C_2H_5	A[a]	**3a** (77)
CH_3	n-C_4H_1	A	**3b** (80)
CH_3	n-C_6H_{13}	A	**3c** (73)
n-C_4H_9	n-C_4H_9	A	**3d** (68)
n-C_4H_9	CH_3	B[b]	**3b** (91)
n-C_6H_{13}	CH_3	B	**3c** (73)

[a] Alkyllithium was reacted with the ketone (-40 °C, 1 h), and a mixture 1.5 parts of $(CH_3)_2Zn$ and 2.0 parts of $TiCl_4$ in CH_2Cl_2 (this generates a 1:1 mixture of **5** and **6**) was added at -40 °C. The reaction mixture was allowed to come to -10 °C (2 h) and then poured onto ice-water. Extraction and Kugelrohr distillation afforded **3**. [b] The ketone was reacted with **6** in CH_2Cl_2 at -40 to -10 °C (2 h) according to the literature procedure.[7]

Experimental Section

Materials. Ketones **7** were prepared according to literature procedures (**7**, R^1 = methyl;[8] **7**, R^1 = *n*-butyl or *n*-hexyl[9]).

Preparation of a Mixture of CH_3TiCl_3 (5) and $(CH_3)_2TiCl_2$ (6). Stock solutions of a 1:1 mixture of **5** and **6** were prepared by adding 150 mm of $(CH_3)_2Zn$[10] to 200 mmol of $TiCl_4$ in 300 mL dry CH_2Cl_2 under an atmosphere of nitrogen at -30 °C.

Geminal Dialkylation of Ketones 7 (Method A). To 10 mmol of ketones **7** in 10 mL of dry hexane was added 10.5 mmol of alkyllithium in hexane at -40 °C under nitrogen. After 1 h the precipitated lithium alcoholate **8** was taken up in 40 mL of dry CH_2Cl_2. At -40 °C, 36 mL of the above stock solutions, of **5** and **6** were added, and the mixture was stirred for 2 h while the temperature was allowed to come to -10 °C. [Instead of using stock solutions of **5** and **6**, one can add the corresponding amounts of $(CH_3)_2Zn$ and $TiCl_4$ simultaneously to **8**; this has no effect on the yields.] The mixture was poured onto ice-water, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2.

(1) Reviews of tetrahydrocannabinoid chemistry: Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75. Mechoulam, R.; Carlini, E. A. *Naturwissenschaften* **1978**, *65*, 174.

(2) Petrzilka, T.; Haeflinger, W.; Sikemaier, C. *Helv. Chim. Acta* **1969**, *52*, 1102. Matsumoto, K.; Stark, P.; Meister, R. G. *J. Med. Chem.* **1977**, *20*, 17.

(3) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277.

(4) Singh, V.; Kane, V. V.; Martin, A. R. *Synth. Commun.* **1981**, 429.

(5) Review of these and other organotitanium reagents: Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. See also "Gmelin Handbuch, Titanorganische Verbindungen"; Springer-Verlag, New York, 1979; Vol. 40.

(6) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 901.

(7) Reetz, M. T., Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* **1981**, 237.

(8) Cram, D. J. *J. Am. Chem. Soc.* **1948**, *70*, 4246.

(9) Suter, C. M.; Weston, A. W. *J. Am. Chem. Soc.* **1939**, *61*, 232.

(10) Large-scale quantities of dimethylzinc were synthesized (by the method of: Renshaw, R. R.; Greenlow, C. E. *J. Am. Chem. Soc.* **1920**, *42*, 1472) from CH_3I and a Zn/Cu couple prepared from zinc powder and copper citrate (Kung, R. C.; Tang, P. J. C. *Ibid.* **1954**, *76*, 2262).

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The combined organic phases were dried over Na_2SO_4, the solvent was stripped off, and the residue was Kugelrohr distilled to provide compounds **3** (Table I).

Geminal Dimethylation of Ketones 7 (Method B). $TiCl_4$ (4.6 mL, 42 mmol) in 80 mL of CH_2Cl_2 was treated with 14 mL of a 3 M solution of $(CH_3)_2Zn$[10] in CH_2Cl_2 at −40 °C under nitrogen, and the mixture was stirred for 10 min. At that temperature 20 mmol of ketone **7** was slowly added and the mixture stirred for 2 h while the temperature was slowly allowed to come to −10 °C. The reaction mixture was then worked up as above (for yields of **3**, see Table I).

Spectroscopic and Analytic Data. 5-(1,1-Dimethylpropyl)resorcinol Dimethyl Ether (3a): Kugelrohr distillation at an 80 °C oven temperature and 0.1 torr; ^1H NMR (CCl_4) δ 0.7 (s, 3), 1.25 (s, 6), 1.63 (q, 2), 3.9 (s, 6), 6.05 (d, 1), 6.2 (d, 2); IR (neat) 2985, 1600, 1205, 1155, 695 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.02; H, 9.61. Found: C, 75.20; H, 9.75.

5-(5-Methylnon-5-yl)resorcinol Dimethyl Ether (3d): Kugelrohr distillation at a 130 °C oven temperature and 0.1 torr; ^1H NMR (CCl_4) δ 0.82 (t, 6), 1.2 (s, 3), 1-1.7 (m, 12), 3.7 (s, 6), 6.2 (br s, 1), 6.35 (br s, 2); IR (neat) 2980, 2940, 1595, 1460, 1205, 1160, 705 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.71; H, 10.78. Found: C, 78.01; H, 10.90.

Data for compounds **3b** and **3c** correspond to literature values.[2]

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft und the Fonds der Chemischen Industrie.

Registry No. 3a, 83816-35-7; **3b**, 22930-08-1; **3c**, 60526-81-0; **3d**, 83816-36-8; **5**, 2747-38-8; **6**, 35739-70-9; **7** (R^1 = CH_3), 39151-19-4; **7** (R^1 = $CH_3(CH_2)_3$), 5333-29-9; **7** (R^1 = $CH_3(CH_2)_5$), 39192-51-3; **8a**, 83816-37-9; **8b**, 83816-38-0; **8c**, 83816-39-1; **8d**, 83816-40-4; CH_3CH_2Li, 811-49-4; $CH_3(CH_2)_3Li$, 109-72-8; $CH_3(CH_2)_5Li$, 21369-64-2.

Synthesis of Spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,2′-oxiranes] and Spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-ones] and the Use of Carbon-13 Nuclear Magnetic Resonance Spectroscopy in the Assignment of Stereochemistry to Epoxides[1]

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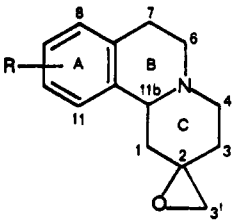
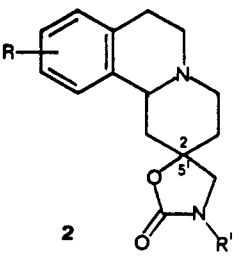
We required substituted spiro epoxides **1** as intermediates for making derivatives of the spiro[1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-2,5′-oxazolidin-2′-one] system **2**.[2] The preparation of epoxide **3** had been reported by Popp;[3,4] however, there was no assignment given to the relative stereochemistry of the three asymmetric centers in this compound. Since we required methodology for making compounds such as **2** with defined stereochemistry at the spiro fusion point, we have examined the precursor system **1** in greater detail. We now report stereoselective methods for the preparation of both diastereoisomers of epoxide **1**, the subsequent transformation of these epoxides into the separate isomers of spiro compounds **2**, and the application of ^{13}C NMR spectroscopy to the assignment of stereochemistry to epoxides such as **1**.



1



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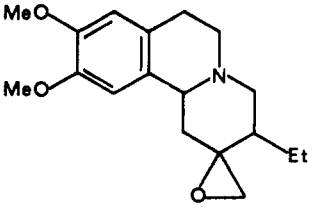
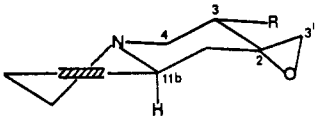


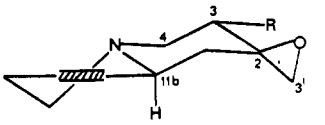
3

The preparation of epoxides was achieved according to Scheme I. Reaction of ketone **4**[5] with oxosulfonium ylide **5** gave the crystalline epoxide **6** in 45% yield. Sulfonium ylide **7** combined with **4** to give a ca. 1:4 mixture of **6** and isomer **8** in 69% yield. The crystalline isomer **8** was isolated in 27% yield by trituration of the mixture with hot hexane. In our hands the ylide **5** reacted with ketone **9**[6] to give a 93% yield of **3a** as compared to 67% reported in the literature.[3] Reaction of **9** with **7** gave a ca. 6:1 mixture of **3a** and **3b** in 82% yield. We were not able to isolate pure **3b** from this mixture.

The stereochemical assignments given to **6**, **8**, and **3a,b**



6 : R = H



8 : R = H

3a : R = Et

3b : R = Et

are founded on the stereoselective preferences of ylides **5** and **7** as originally determined by a study of the products obtained from their reaction with 4-*tert*-butylcyclohexanone.[7] The argument used to assign stereochemistry to **6** and **8** states that the stabilized oxosulfonium ylide **5** gives the product of thermodynamic control, one which contains a pseudoequatorial methylene. The more reactive sulfonium ylide **7** gives the product mixture of kinetic control, since its addition to a carbonyl is less reversible than is the case with ylide **5**.[8] The reactivity of **7** leads to two products (**3a** and **3b**) from reaction with **9**, whereas the less reactive, and thus more selective, ylide **5** reacts with α-ethyl-substituted ketone **9** to give a single product, which is assigned structure **3a** (Popp's epoxide **3**) on the basis of the assumption that it is the product of thermodynamic control and that it therefore contains the ethyl

(1) Contribution No. 620 from the Institute of Organic Chemistry.
(2) A substituted example of heterocyclic system **2** has been reported in the literature: Maillard, J.; Langlois, M.; DeLaunay, P.; Vo Van, T.; Chenu, J.; Morin, R.; Benharkate, M.; Manuel, C.; Montoso, F. *J. Med. Chem.* **1972**, *15*, 1123.
(3) Popp, F. D.; Watts, R. F. *J. Pharm. Sci.* **1978**, *67*, 871.
(4) Popp, F. D.; Watts, R. F. *J. Heterocycl. Chem.* **1978**, *15*, 675.
(5) Beke, D.; Szantay, C. *Chem. Ber.* **1962**, *65*, 2132.
(6) Oppenshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1449.
(7) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(8) House, H. O. "Modern Synthetic Reactons", 2nd ed.; W. A. Benjamin: Menlo Park, CA, **1972**, p 718.

0022-3263/83/1948-0255$01.50/0