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SYNTHESIS OF SUBSTITUTED SPIRO[4.5]DECA-3,6,9-TRIENE-2,8-DIONES: AN EXPEDITIOUS ROUTE TO THE SPIRO[4.5]DECANE TERPENE SKELETON

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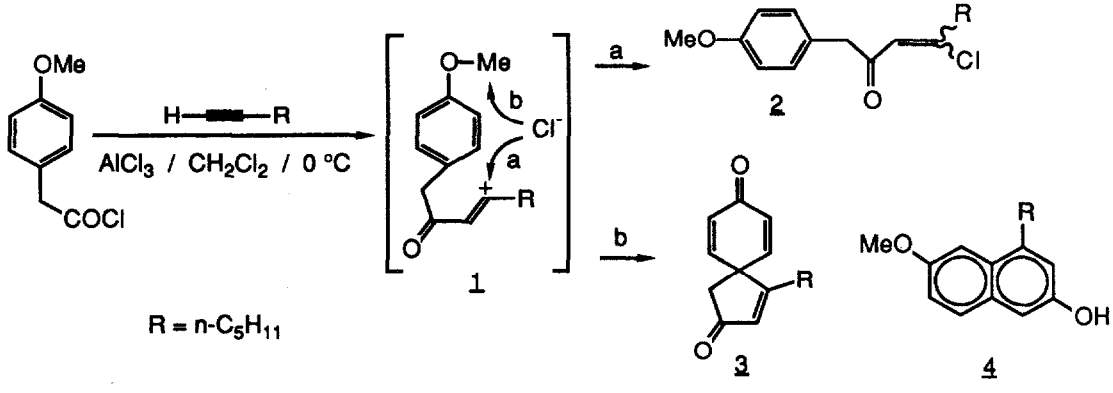
Summary: Substituted spiro[4.5]decanes are prepared in two steps in fair to moderate yield. A substituted 4-methoxyphenylacetyl chloride, prepared from the corresponding acid, is reacted with a substituted acetylene (or acetylene gas) in the presence of aluminum chloride in methylene chloride at 0 °C to produce the corresponding substituted spiro derivative.

The spiro[4.5]decane ring system is a key structural feature possessed by a number of sesquiterpenes including the spirovetivanes, acorones, and alaskanes.[1] A number of these substances are phytoalexins, defensive chemical agents produced by plants in response to an infecting organism.[2] The sterically congested quaternary carbon center along with the interesting biological activity possessed by these molecules has drawn the attention of synthetic chemists in recent years, and a variety of cyclization techniques have been employed for the construction of the spiro skeleton of these natural products.[1,3] In this letter we report an extremely simple route to the spiro[4.5] ring system.

During a study concerning the synthesis of aryl-β-chlorovinyl ketones[4], we found that treatment of 4-methoxyphenylacetyl chloride with 1-heptyne in the presence of aluminum chloride in methylene chloride at 0 °C, contrary to literature precedent[4], produced none of the expected α-p-methoxyphenylmethyl-β'-chlorovinyl ketone 2 (SCHEME 1, pathway a). Instead, the major product was the substituted spiro derivative 3 isolated in 42% yield. This product probably arose from intramolecular electrophilic attack at the 1 position of the electron rich aromatic nucleus by an intermediate vinyl cation 1 with the concomitant loss of methyl chloride (SCHEME 1, pathway b). Apparently, the electron releasing property of the p-methoxy moiety plays an important role in the outcome of the reaction since electron withdrawing groups[5] (nitro and carboalkoxy) present on the aromatic nucleus deactivate the ring toward intramolecular electrophilic attack and afford the expected chlorovinyl ketones (2) as the major products.

SCHEME 1



In order to determine the generality of this procedure, 4-methoxyphenylacetyl chloride was allowed to react with a variety of acetylenes. A study was also conducted to determine if substitutions could be tolerated on the 4-methoxyphenylacetic acid substrate. We were especially interested in subjecting to the reaction conditions a 4-methoxyphenylacetyl chloride substituted at the 2 and 6 positions since several of the naturally occurring sesquiterpenes bear substituents at these positions. We were pleased to discover that steric bulk at the 2 and 6 positions had little influence on the cyclization (entry 3i). As can be seen in Table 1 this reaction is general and allows the presence of a large range of functionality and a variety of possible substitutions in both the acetylenic precursor and the 4-methoxyphenylacetic acid moiety.

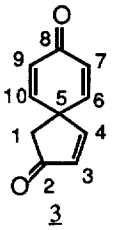
In most of the cases studied, the TLC of the crude reaction mixture appeared quite complex. However, the spiro product was easily distinguished from other reaction by-products by visualization of the TLC plate with 2,4-dinitrophenylhydrazine (2,4-DNP) indicator solution[6], producing bright red to orange spots. Other products isolated from some of the experiments included small amounts of the expected chlorovinyl ketone 2 (stains light yellow with 2,4-DNP solution) and small amounts of substituted β-napthols 4[7] (stains brick red with 2,4-DNP solution). The small amounts of β-napthols (4) observed were probably formed by attack of the intermediate vinyl cation 1 at the 2 position of the aromatic nucleus.[8] Although the reaction afforded variable yields of spiro product (14% to 92% based on the starting acid (two steps)), the procedure is simple to carry out and allows for the preparation of substituted ring systems that might be unattainable by other methods.

The procedure is general for substituted 4-methoxyphenylacetyl chlorides and substituted acetylenes and is outlined here for the preparation of the unsubstituted parent spiro ring system, spiro[4.5]deca-3,6,9-triene-2,8-dione (3b). A round bottom flask equipped with a magnetic stirrer was charged with 4-methoxyphenylacetyl chloride[9] (15 mmol), and methylene chloride (50 ml). The solution was saturated with acetylene gas[10] which was introduced from a balloon. The solution was then cooled to 0 °C and aluminum chloride (5.4 g, 40 mmol) was added portionwise over 15 minutes. The reaction mixture was then stirred under an atmosphere of acetylene for 1 hour at 0 °C. After this time the reaction was quenched with ice and the mixture was poured into water and extracted with ether. The extract was washed successively with water, saturated aqueous sodium bicarbonate, saturated brine, and then dried over magnesium sulfate. After removal of the solvents *in vacuo*, the crude product was chromatographed on silica gel (gradient elution with ether-hexane from 1:1 to 100% ether) to afford 3b in 37% yield.

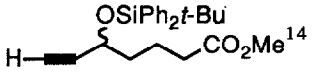
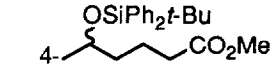
Acknowledgements:

We are indebted to Dr. Jeremy D. Hribar and Ms. Lydia Swenton for spectral interpretation and Drs. Stevan W. Djurić, Thomas D. Penning, Professors Anthony G. M. Barrett, Paul A. Grieco, Peter Beak, and Bruce Lipshutz for many helpful discussions.

Table 1. Preparation of substituted spiro[4.5]decanes (3):



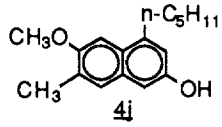
3

Entry	Acetylene	Product (3)[11]	Yield (%)[12]	Mp (°C)[13]
a	n-heptyne	4-n-C_5H_{11}	42	100-101
b	acetylene	unsubstituted	37	165-167
c	phenylacetylene	4-phenyl	92	109-110
d			32	oil
e	1,4-bis(trimethylsilyl)-1,3-butadiyne	3-TMS-4-C≡C-TMS	32	119-121
f	1,4-bis(trimethylsilyl)-1,3-butadiyne†	3-TMS-4-C≡C-H	52	98-100
g	1,7-octadiyne††	4,4'-$(CH_2)_4$-	14	150 decomp.
h	6-dodecyne	3,4-di-(n-C_5H_{11})	42	oil
i	acetylene†††	6,10-dimethyl	38	161-163
j	n-heptyne††††	4-n-C_5H_{11}-7-methyl	48	97-98

† Reaction run at reflux.
†† Reacted with 2 equivalents of 4-methoxyphenylacetyl chloride.
††† Reacted with 4-methoxy-2,6-dimethylphenylacetyl chloride.[15]
†††† Reacted with 4-methoxy-3-methylphenylacetyl chloride.[16]

References and Notes:

1) For a review see: C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White, p. 264, in J. ApSimon, "The Total Synthesis of Natural Products", Vol. 5, Wiley-Interscience, New York, 1983.
2) C. J. W. Brooks and D. G. Watson, Nat. Prod. Rep., **2**, 427 (1985).
3) C. Iwata, M. Yamada, T. Fusaka, K. Miyashita, A. Nakamura, T. Tanaka, T. Fujiwara, and K. Tomita, Chem. Pharm. Bull., **35** (2), 544 (1987).
4) For a discussion of this reaction see: C. D. Nenitzescu and A. T. Balaban, p. 1081, in G. Olah, "Friedel-Crafts and Related Reactions", Vol. 3, Pt. 2, Wiley-Interscience, New York, 1964.
5) Further studies will be reported in a future communication.
6) A. J. Gordon and R. A. Ford, "The Chemist's Companion: A Handbook of Practical Data,Techniques, and References", p. 378, Wiley-Interscience, New York, 1972.
7) For example: During the preparation of 3j, 4j was isolated (*ca.* 5% yield). 4j: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 7.39 (s, 1H), 7.13 (s, 1H), 6.88 (s, 2H), 5.01 (s, 1H), 3.91 (s, 3H), 2.93 (t, 2H, *J*=9), 2.33 (s, 3H), 1.74 (m, 2H), 1.39 (m, 4H), 0.90 (t, 3H, *J*=7).



4j

8) At the suggestion of a referee, the products of the reaction were individually subjected to the reaction conditions in order to rule out product interconversion. This was carried out with entry j. The spiro product 3j as well as the napthol 4j and the chlorovinyl ketones (both isomers) 2j all remained unchanged when

exposed to the reaction conditions (2.2 equiv. $AlCl_3$, CH_2Cl_2, 0 °C, 1 hr.). This result suggests that we are observing a kinetic product distribution and direct intramolecular attack of the aromatic ring to form the napthol was probably occurring.

9) Prepared from 4-methoxyphenylacetic acid (2.5 g, 15 mmol), oxalyl chloride (3 ml, 34.4 mmol), and a catalytic amount of dimethyl formamide in benzene (50 ml). The mixture was stirred 3 hours at room temperature until gas evolution ceased. The volatile components were then removed *in vacuo* and the product was used in the next step without further purification.

10) Other acetylenes (1 equiv.) were added neat to the acid chloride in methylene chloride prior to the addition of aluminum chloride.

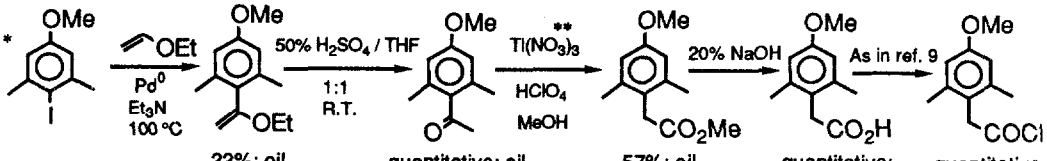
11) **NMR Data:**
3a: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 6.72 (d, 2H, *J*=10), 6.45 (d, 2H, *J*=10), 6.22 (s, 1H), 2.66 (s, 2H), 2.12 (t, 2H, *J*=10), 1.55 (m, 2H), 1.30 (m, 4H), 0.89 (t, 3H, *J*=7).
3b: ^{1}H NMR: (400 MHz, $CDCl_3$,) δ 7.22 (d, 1H, *J*=5.8), 6.73 (d, 2H, *J*=10), 6.42 (d, 1H, *J*=5.8), 6.38 (d, 2H, *J*=10), 2.63 (s, 2H).
^{13}C NMR: (100 MHz, $CDCl_3$,) δ 205.7 (C-2), 184.3 (C-8), 163.8 (C-4), 149.2 (C-6,10), 135.1 (C-3), 129.8 (C-7,9), 49.5 (C-5),43.9 (C-1).
3c: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 7.6-7.3 (m, 5H), 6.96 (d, 2H, *J*=10), 6.71 (s, 1H), 6.47 (d, 2H, *J*=10), 2.80 (s, 2H).
3d: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 7.65-7.33 (m, 10H), 6.66 (dd, 1H, *J*=4, 10), 6.58 (s, 1H), 6.25 (dd, 1H, *J*=4, 10), 6.03 (dd, 1H, *J*=4, 10), 5.53 (dd, 1H, *J*=4, 10), 4.23 (t, 1H, *J*=3), 3.65 (s, 3H), 2.45 (dd, 2H, *J*=20, 40), 2.35-2.10 (m, 2H), 1.85-1.40 (m, 4H), 1.08 (s, 9H).
3e: ^{1}H NMR: (200 MHz, $CDCl_3$,) δ 6.59 (d, 2H, *J*=10), 6.38 (d, 2H, *J*=10), 2.64 (s, 2H), 0.28 (s, 9H), 0.15 (s, 9H).
3f: ^{1}H NMR: (200 MHz, $CDCl_3$,) δ 6.61 (d, 2H, *J*=10), 6.41 (d, 2H, *J*=10), 3.90 (s, 1H), 2.66 (s, 2H), 0.32 (s, 9H).
3g: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 6.65 (d, 4H, *J*=10), 6.45 (d, 4H, *J*=10), 6.18 (s, 2H), 2.66 (s, 4H), 2.10 (m, 4H), 1.56 (m, 4H).
3h: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 6.57 (d, 2H, *J*=10), 6.34 (d, 2H, *J*=10), 2.53 (s, 2H), 2.15 (t, 2H, *J*=9), 2.03 (t, 2H, *J*=9), 1.45-1.10 (m, 12H), 0.85-0.70 (m, 6H).
3i: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 7.17 (d, 1H, *J*=6), 6.54 (d, 1H, *J*=6), 6.27 (s, 2H), 2.54 (s, 2H), 1.89 (s, 6H).
3j: ^{1}H NMR: (300 MHz, $CDCl_3$,) δ 6.69 (dd, 1H, *J*=5, 10), 6.48 (s, 1H), 6.40 (d, 1H, *J*=10), 6.16 (s, 1H), 2.13 (s, 2H), 2.06 (t, 2H, *J*=8), 1.96 (s, 3H), 1.52 (m, 2H), 1.28 (m, 4H), 0.88 (t, 3H, *J*=7).

12) Refers to isolated yields for the two step conversion: acid → acid chloride → spiro derivative. Satisfactory elemental and/or high resolution mass spectral, IR and NMR measurements were obtained for all new compounds.

13) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

14) Prepared in racemic form by substituting a sodium borohydride reduction for the (-)-9-pinanyl-BBN reduction step described in: K. C. Nicolaou, R. E. Zipkin, R. E. Dolle, and B. D. Harris, J. Am. Chem. Soc., **106**, 3748 (1984).

15) Prepared by the sequence:



* S. Goldschmidt and L. Suchanek, Chem. Ber., **90**, 19 (1957).

** A. McKillop, B. P. Swann, and E. C. Taylor, J. Am. Chem. Soc., **93**, 4919 (1971).

16) As in ref. 9 except 4-methoxy-3-phenylacetic acid was used.

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