Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Orthobromodiphenylmethane Derivatives as Starting Materials for the Total Synthesis of Anthraquinones

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Version of record first published: 23 Aug 2006.

To cite this article: Wanda P. Almeida & Paulo R.R. Costa (1996): Orthobromodiphenylmethane Derivatives as Starting Materials for the Total Synthesis of Anthraquinones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:23, 4507-4518

To link to this article: http://dx.doi.org/10.1080/00397919608003853

SYNTHETIC COMMUNICATIONS, 26(23), 4507-4518 (1996)

ORTHOBROMODIPHENYLMETHANE DERIVATIVES AS STARTING MATERIALS FOR THE TOTAL SYNTHESIS OF ANTHRAQUINONES

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ABSTRACT: In this communication we describe the synthesis of four simple anthraquinones by a five-step sequence, using easily available bromobenzaldehydes and phenyllithium derivatives as starting materials.

As part of a research program aiming at the synthesis of biologically active, aromatic natural products, we described some years ago[1] a new method for preparing phthalides (scheme 1, e.g. **2**) by addition of aryllithium species to **1**. Compound **2b** was used as intermediate in the total synthesis of a naturally occurring furonaphtoquinone[2].

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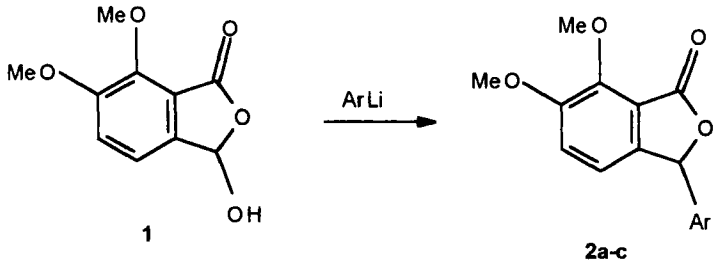
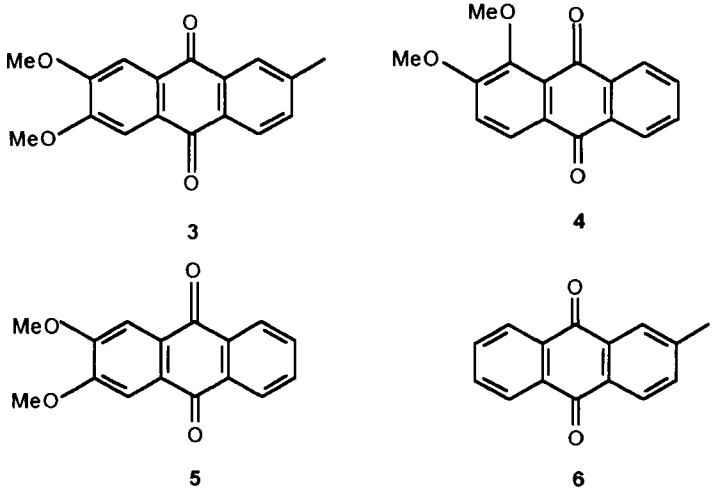
SCHEME 1



a: Ar = 2-furyllithium; **b**: Ar = 5-ethyl-2-furyllithium; **c**: Ar = 2-lithiumthiophene.

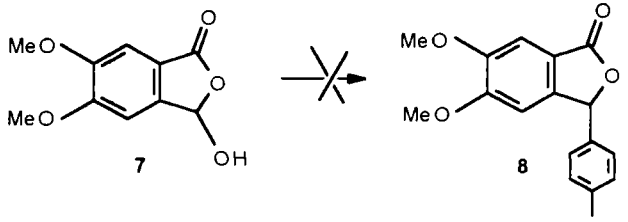
In connection with that research, we decided to prepare anthraquinones **3-6** (fig. 1), by essentially the same methodology. As first target we chose the anthraquinone **3**, a substance isolated from *Hedyotis diffusa* (Rubiaceae), extracts of which have been used in Chinese and Indian folk medicine[3].

FIG.1: Anthraquinones Synthesized in this Work



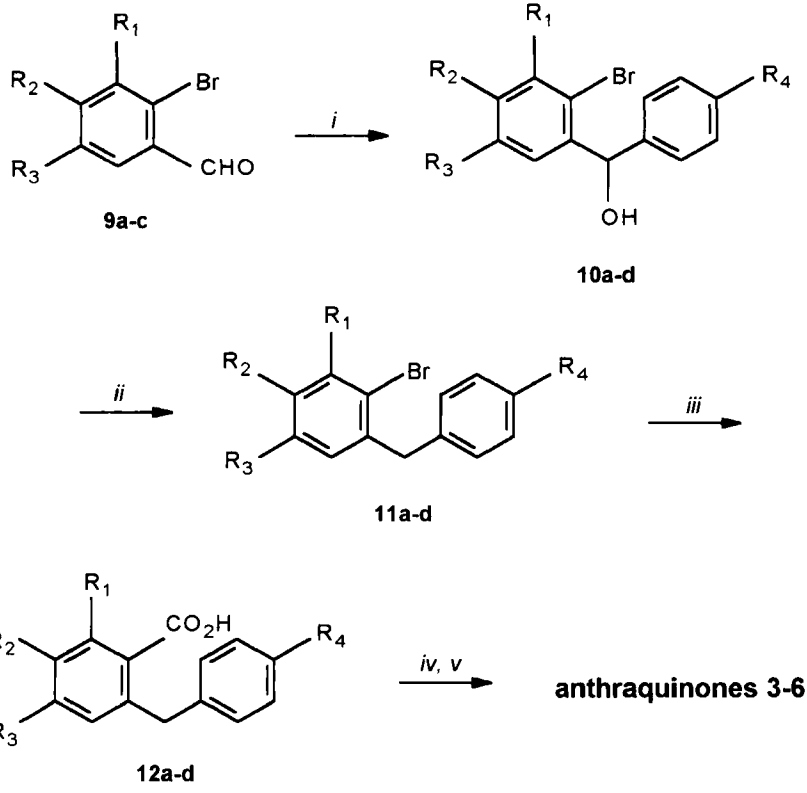
We therefore prepared the hydroxyphtalide **7** in accord with the precedent literature[2], and treated it with *p*-tolyllithium. However all our attempts to obtain **8** led only to the starting material (scheme 2).

SCHEME 2



These results lead us to envisage another approach to obtain the target anthraquinones. It relies on the use of *o*-bromodiphenylmethane derivatives (**10a-d**) as starting materials (scheme 3). The addition of phenyl or *p*-tolyllithium, to the suitable bromobenzaldehydes (**9a,b or c**) furnished the the desired bromoalcohols in good yield. The benzyl hydroxy group in **10a-d** was removed by the Gribble's procedure[4] ($NaBH_4$/TFA), leading to **11a-d** in good yield. Bromo-lithium exchange in **11a-d**, followed by trapping of the resulting aryllithium derivatives with CO_2 led to the acids **12a-c**. Having constructed the requisite skeletons, we then carried out the necessary functional transformations: intramolecular Friedel-Crafts acylation (TFAA/CH_2Cl_2), folllowed by oxidation (CrO_3/AcOH) of crude products afford the anthraquinones **3-6**. Overall yields from bromobenzaldehydes are shown in the Table. All spectral data for **3**[3], **4**[8] and **6**[9], are in accord with precedent

SCHEME 3



9a: R_1 = H, R_2 = R_3=OMe; **9b**: R_1 = R_2 = OMe, R_3 = H; **9c**: R_1 = R_2 = R_3 = H.
10a: R_1 = H, R_2 = R_3 = OMe, R_4 = Me; **10b**: R_1 = R_2 = OMe, R_3 = R_4 = H; **10c**: R_1 = R_4 = H, R_2 = R_3 =OMe; **10d**: R_1 = R_2 = R_3 = H, R_4 = Me;
11a: R_1 = H, R_2 = R_3 = OMe, R_4 = Me; **11b**: R_1 = R_2 = OMe, R_3 = R_4 = H; **11c**: R_1 = R_4 = H, R_2 = R_3 =OMe; **11d**: R_1 = R_2 = R_3 = H, R_4 = Me;
12a: R_1 = H, R_2 = R_3 = OMe, R_4 = Me; **12b**: R_1 = R_2 = OMe, R_3 = R_4 = H; **12c**: R_1 = R_4 = H, R_2 = R_3 =OMe; **12d**: R_1 = R_2 = R_3 = H, R_4 = Me.

Reagents: *i*: *p*-tolyllithium/THF(-85 °C) to obtain **10a** or **10d**; phenyllithium to obtain **10b** or **10c**; *ii*: $NaBH_4$/TFA, 10-15 °C; *iii*: nBuLi/THF,-78 °C; CO_2, then H_3O^+; *iv*: TFAA, CH_2Cl_2, 0 °C; *v*: CrO_3/AcOH, 0 °C →r.t.

literature. For anthraquinone **5**, these data are not available in the literature[10].

The classical synthesis of anthraquinones involves, in general, Diels-Alder approach[5], double Friedel - Crafts condensation of phthalic acids derivatives with phenols or phenolethers[6], or direct metalation of *N,N*-diethylbenzamides[7], followed by trapping with suitable electrophile and cyclization to the correspondent phthalide, but our strategy is complementar to those ones, employing easily available starting materials.

TABLE

ANTHRAQUINONES	OVERALL YIELD (%)
3	47*
4	68
5	51
6	50

* First synthesis[3]: 15% overall yield.

EXPERIMENTAL

General: 6-Bromoveratraldehyde, 2-Bromobenzaldehyde, phenyllithium and *n*BuLi were purchased from Aldrich Chemical Co. 2-bromo-3,4-dimethoxybenzaldehyde was prepared from isovanilin[11]. "Usual work up" means, drying over Na_2SO_4, filtration, concentration *in vacuum*, column chromatography (silica gel) and solvent evaporation (reduced pressure).

Tetrahydrofuran and CH_2Cl_2 were distilled from sodium benzophenone ketyl and CaH_2, respectively. Melting points (uncorrected) were determined on a Büchi 510 apparatus. ^{1}H-NMR spectra ($CDCl_3$/TMS) were recorded on a Varian XL-100 (100MHz) spectrometer. Infrared spectra were obtained on a Nicolet FT-IR 510. MS spectra were determined on a VG MM 12.

***o*-Bromodiphenylmethanol derivatives 10a and 10d** :To a stirred solution of *p*-iodotoluene (1.2 mmol), in dry THF (2 mL), under N_2, at -85 °C, 0.9 mL (1.45 mmol) of 1.6 M solution of *n*BuLi, was added dropwise. After 15 min., bromoaldehyde (**9a** or **9c**) in THF (1.57 mmol in 4 mL), was added. The mixture was warmed to room temperature after the addition was complete, then diluted with H_2O (20 mL) and extracted with EtOAc. After usual work-up **10a** (66%yield) and **10d** (88%yield) were obtained.

10a:

bp (12 mmHg): 80-81 °C

^{1}H-NMR: δ 7.30-7.05 (m, 5H); 6.95 (s, 1H); 6.05 (s, 1H); 3.85 (s, 6H); 2.30 (s, 3H) ppm. **IR** (neat): ν 3410, 3027, 2840, 1600 cm^{-1}. **MS** (%): m/z 338 (81) [M^+ + 2]; 336 (86) [M^+]; 245 (52); 138 (67); 119 (100). M^+·Calcd. for $C_{16}H_{17}BrO_3$: 336.0361; Found:336.0357.

10d:

bp (15 mmHg): 93-95 °C

^{1}H-NMR: δ 7.30-7.05 (m, 8H); 6.00 (s, 1H); 2.30 (s, 1H) ppm. **IR** (neat): ν 3406, 3020, 2827, 1598 cm^{-1}. **MS** (%): m/z 278 (76) [M^+ + 2]; 276 (78) [M^+]; 260 (35); 261 (40); 184 (65); 119(100). M^+·Calcd. for $C_{14}H_{13}BrO$: 276.0149; Found: 276.0159.

o-Bromodiphenylmethanol derivatives 10b and 10c: To a solution of bromoaldehyde in dry THF (2.5 mmol in 10 mL), under N_2, at 0 °C, a 1.8 M solution of phenyllithium (1.8 ml, 3.25 mmol) was added. The mixture was warmed to room temperature and kept under stirring for 3h, then diluted with water (20 mL).The desired bromoalcohols (**10b**: 86%, **10c**: 75%) were obtained after following the same procedures and work up described above.

10b:

bp (15 mmHg): 78-80 °C

^{1}H-NMR: δ 7.2-6.9 (m, 7H); 6.05 (s, 1H); 3.85 (s, 6H) ppm. **IR** (neat): ν 3410, 3020, 2846, 1600 cm^{-1}. **MS** (%): m/z 324 (74) [M^+ + 2]; 322 (76) [M^+]; 292 (35); 245 (36); 105 (100). M^+·Calcd. for $C_{15}H_{15}BrO_3$: 322.0204; Found: 322.0196.

10c:

bp (10 mmHg): 85-86 °C

^{1}H-NMR :δ 7.30-7.05 (m, 8H); 6.00 (s, 1H); 3.80 (s, 6H) ppm. **IR** (neat): ν 3415, 3022, 2838, 1601 cm^{-1}. **MS** (%): m/z 324 (70) [M^+ + 2]; 322 (68) [M^+]; 260 (33); 245 (54); 105 (100). M^+·Calcd. for $C_{15}H_{15}BrO_3$: 322.0204; Found: 322.0208.

Reduction of bromoalcohols 10: To magnetically stirred TFA (7.5 mL), at 0 °C under N_2 was added in portions (*carefully*) powdered $NaBH_4$ (329 mg = 8.67 mmol). To the resulting mixture at 10-15 °C was added a solution of the bromoalcohol (2.08 mmol) in dry CH_2Cl_2 (10 mL). A red-orange coloration developed, and the mixture was stirred overnight at room temperature. Dilution with cold water, basification with NaOH pellets and extraction with

CH_2Cl_2 gave, after washing (water, brine, water) and usual work up, the bromides **11a** (93%), **11b** (95%), **11c** (96%) and **11d** (88%) were obtained.

11a:

bp (10 mmHg): 96-98 °C

^{1}H-NMR: δ 6.85 (m, 5H); 6.40 (s, 1H); 3.85 (s, 2H); 3.80 (s, 3H); 3.70 (s, 3H); 2.25 (s, 3H) ppm. **IR** (neat): ν 3020, 2940, 2830, 1604cm^{-1}. **MS** (%): m/z 322 (97) [M^+ + 2]; 320 (100) [M^+]; 305 (15); 241 (87); M^+·Calcd. for $C_{16}H_{17}BrO_2$: 320.0412; Found: 320.0816.

11b:

bp (10 mmHg): 68-69 °C

^{1}H-NMR: δ 7.30-7.15 (m, 7H);3.85 (s, 2H); 3.80 (s, 3H); 3.75 (s, 3H) ppm. **IR** (neat): ν 3010, 2955, 2820, 1602 cm^{-1}. **MS** (%): m/z 308 (82) [M^+ + 2]; 306 (80) [M^+]; 276 (85); 157 (65); 91 (100). M^+·Calcd. for $C_{15}H_{15}BrO_2$: 306.0255; Found: 306.0258.

11c:

bp (10 mmHg): 60-61 °C

^{1}H-NMR: δ 6.85 (m, 6H); 6.35 (s, 1H); 3.85 (s, 2H); 3.80 (s, 3H); 3.70 (s, 3H) ppm. **IR** (neat): ν 3008, 2960, 2822, 1601 cm^{-1}. **MS** (%): m/z 308 (74) [M^+ + 2]; 306 (76) [M^+]; 169 (45); 157 (60); 91 (100). M^+·Calcd. for $C_{15}H_{15}BrO_2$: 306.0255; Found: 306.0251.

11d:

bp (10 mmHg): 65-66 °C

^{1}H-NMR: δ 7.1 (m, 8H); 3.80 (s, 2H); 2.30 (s, 1H) ppm. **IR** (neat): ν 3022, 2940, 2822, 1603 cm^{-1}. **MS** (%): m/z 262 (73) [M^+ + 2]; 260 (75) [M^+]; 241 (80); 105 (100); M^+·Calcd. for $C_{14}H_{13}Br$: 260.0201; Found: 260.0208.

Halogen-metal exchange and Carboxylation: *n*BuLi (1.92 mmol) was added dropwise to a solution of bromide (1.4 mmol) in THF (5ml), at -78 °C, under stirring. After 40 min. the red suspension was treated with dried CO_2 (gas) for 30 min. The resulting white mixture was warmed to room temperature, and diluted with water (30 mL). After washing with Et_2O (3 x 10 mL) and removal of the organic layers, the aqueous layer was adjusted with HCl conc. to pH 1 and extracted with EtOAc (6 x 15 mL). The combined organic layers were concentrated and, after usual work up the acids **12** were obtained. Recrystallization (EtOAc-Hex 1%) furnished analytical samples (**12a**, 85%; **12b**, 90%, **12c**, 80% and **12d**, 75%).

12a:

mp: 89-90 °C.

^{1}H-NMR: δ 12.8 (br, 1H); 7.5-6.9 (m, 6H); 3.90 (s, 2H); 3.85 (s, 6H); 2.30 (s, 3H) ppm. **IR** (KBr): ν 3500-2500, 1686, 1671, 1598 cm^{-1}. **MS** (%): m/z 286 (70) [M^+]; 285 (12); 241 (100); 105 (60). M^+·Calcd. for $C_{17}H_{18}O_4$: 286.1205; Found: 286.1199.

12b:

mp:176-178 °C

^{1}H-NMR: δ 11.8 (br, 1H); 7.45-7.15 (m, 7H); 3.95 (s, 2H); 3.85 (s, 3H); 3.75 (s, 3H) ppm. **IR** (KBr): ν 3550-2580, 1685, 1675, 1600 cm^{-1}. **MS** (%): m/z 272 (58) [M^+]; 271 (8); 227 (100); 91 (32). M^+·Calcd. for $C_{16}H_{16}O_4$: 272.1049; Found: 272.1057.

12c:

mp:86-88 °C

^{1}H-NMR: δ 10.9 (br, 1H); 7.5-6.8 (m, 6H); 3.90 (s, 2H); 3.85 (s, 6H) ppm. **IR**

(KBr): ν 3508-2543, 1685, 1673, 1600 cm^{-1}. **MS** (%): m/z 272 (65) [M^+]; 271 (52); 227 (100); 91 (27). M^+·Calcd. for $C_{16}H_{16}O_4$: 272.1048; Found: 272.1042.

12d:

mp: 113-114 °C

^{1}H-NMR: δ 11.8 (br, 1H); 8.0-7.85 (m, 4H); 7.3-7.1 (m, 4H); 4.40 (s, 2H); 2.25 (s, 3H) ppm. **IR** ($CHCl_3$): ν 3510-2590, 1685, 1670, 1601 cm^{-1}. **MS** (%): m/z 226 (37) [M^+]; 221 (15); 177 (100); 105 (65); M^+·Calcd. for $C_{15}H_{14}O_2$: 226.0994; Found: 226.1008.

Acylation: Trifluoroacetic anhydride (TFAA, 2 mL) was added to a solution of the acid (3.80 mmol) in dry CH_2Cl_2 (30 mL), under N_2, at 0 °C. The mixture was then warmed to room temperature and kept under stirring overnight. After dilution with methanol (20 mL), the solvents were removed *in vacuum* and methanol (20 mL) was added to the crude residue. The solvent was removed *in vacuum* and a new portion of methanol (20 mL) was added. After evaporation, CH_2Cl_2 was added to the residue, and the resulting solution washed with $NaHCO_3$ (10%aq.) and water. The organic layer was separated and worked-up. The crude oil was used in the next step (oxidation) without additional purification. **Oxidation**: A solution of CrO_3 (3.60 mmol) in AcOH (25 mL) and water (30 mL) was added to the crude oil in AcOH (5 mL), under vigorous stirring, at room temperature. After 3h, the mixture was diluted with H_2O (25 mL), carefully neutralized with $NaHCO_3$ (10%aq.) and extracted with CH_2Cl_2 (5 x 15 mL). The combined organic layer was concentrated and worked-up. The solid obtained was purified by TLC employing: EtOAc-Hex. 5% (anthraquinone **3**), EtOAc-Hex. 15%,

anthraquinones **4**, **5** and **6**) as eluents. Yields: **3**: 90%; **4**: 92%; **5**: 88% and **6**: 87%.

3: (6-Methyl hystazarin-methylether)

mp: 237-238 °C (Lit.[3]: 237-238 °C)

^{1}H-NMR: δ 8.15 (d, *J*=10Hz, 1H); 8.05 (sl, 1H); 7.70 (s, 2H); 7.55 (dd, J=10Hz and 2Hz, 1H); 3.95 (s, 6H); 2.50 (s, 3H) ppm. **IR** (KBr): ν 2920, 1668, 1602, 1504 cm^{-1}. **MS** (%): m/z 282 (100)[M^+]; 267 (20); 239 (25); 211 (40). M^+·Calcd. for $C_{17}H_{14}O_4$: 282.0892; Found: 282.0888.

4 (Alizarin dimethylether):

mp: 212-213 °C(Lit.[8]: 212-214 °C)

^{1}H-NMR: δ 8.30-.7.25 (m, 6H); 4.00 (s, 3H); 3.95 (s, 3H) ppm. **IR** (neat): ν 2928, 1672, 1570, 1335, 1265 cm^{-1}. **MS** (%): m/z [M^+]; 268 (100); 240 (36); 238 (28); 212 (45). HRMS·calcd. for $C_{16}H_{12}O_4$: 268.0735; Found: 268.0730

5 (Hystazarin dimethylether):

mp: 237-238 °C (Lit. [10]: 238-239 °C)

^{1}H-NMR: δ 8.15 (s, 2H); 8.00 - 7.70 (m, 4H); 3.98 (s, 6H) ppm. **IR** (KBr): ν 2932, 1670, 1599, 1509 cm^{-1}. **MS** (%): m/z 268 (100) [M^+]; 240(22); 238 (16); 212 (37). HRMS calcd. for $C_{16}H_{12}O_4$: 268.0736; Found: 268.0732

6 (Tectoquinone):

mp: 178-179 °C (Lit. [9]: 174-177 °C)

^{1}H-NMR: δ 8.30-8.15 (m, 4H); 7.80-7.55 (m, 3H); 2.55 (s, 3H) ppm. **IR** (KBr): ν 3001, 2929, 1678, 1598 cm^{-1}. **MS** (%): m/z 222 (100) [M^+]; 194 (38); 165 (85); 149 (52); M^+·Calcd. for $C_{15}H_{10}O_2$: 222.0681; Found: 222.0689.

ACKNOWLEDGEMENTS: Brazilian National Council of Research (CNPq),

Fundação Jose Bonifacio (FuJB) and Fundação Banco do Brasil (FBB) for financial support.

REFERENCES AND NOTES

1 - Costa, P.R.R.; Lopes, C.C.; Lima,E.L.S.; Monteiro, A.J. *Synth.Commun.*, **1988**, 18, 1731.

2 - Costa, P.R.R.; Lopes, C.C.;Lopes, R.S.C.; Marinho, M.F.G.; Castro, R.N. *Synth.Commun.*, **1988**, 18, 1723.

3 - Ho, T- I ; Chen, G-P.; Lin, Y-C.; Lin,Y-M.; Chen, F-C. *Phytochemistry*, **1986,** 25, 1988. *Chem. Abst.*, 1986, **104**, 2837t.

4 - **a)**Gribble, G.W.; Kelly, W.J.;Sanford, E.E., *Synthesis*, **1978**, 763; **b)**Gribble, G.W.; Leese, R.M.; Evans,B.E., *Synthesis.* **1977**, 172.

5 - Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*,.Pergamon Press, UK, **1990**.

6 - See, for example, Kim, K.S.; Spatz, M.W.; Johnson, F. *Tetrahedron Lett.*, **1979**, 331.

7 - Snieckus, V.; Watanabe, M.; de Silva, S.O., *J.Org.Chem.*, **1979**, 44, 4802.

8 - Biehl, E.R.; Khanapure, S.P.; Reddy, R.T., *J.Org.Chem.*, **1987**, 52, 5685.

9 - Itokawa, H.; Qiao, Y.; Takeya, K., *Phytochemistry*, **1991**, 30, 637. *Chem. Abst.*, 1991, **114**, 18207m.

10 - Savage, J.; Proctor, G.R.; Renfrew, A.H., *J.Chem.Soc.,C*, **1969**, 1000.

11 - Hamman, P.R.; Toth, J.E.; Fuchs, P.L., *J.Org.Chem.*, **1988**, 53, 4694.

(Received in the USA 20 June 1996)