# A General $S_{RN}1$-Based Method for Total Synthesis of Unsymmetrically Hydroxylated 2,2′-Binaphthalenes[1]

René Beugelmans,* Michèle Bois-Choussy, and Qian Tang

*Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif-sur-Yvette, France*

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An $S_{RN}1$ reaction between 2′-haloacetophenones and 2′-acetonaphthone derived enolates is the key step in a straightforward one-pot synthesis of unsymmetrically substituted 2,2′-binaphthyl derivatives **3a–j**.

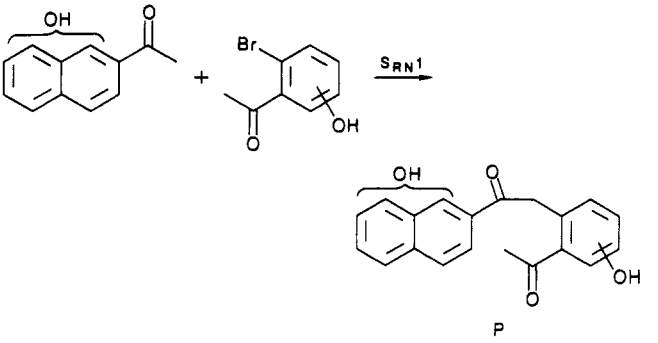
In connection with a research project in the field of bioorganic chemistry, a series of 2,2′-binaphthyl derivatives carrying hydroxyl groups differently located on each naphthalenic subunit was required. Many synthetic methods known to give cross-coupling products from variously functionalized benzenes[2,3] have been applied to naphthalenes and have afforded symmetrical or unsymmetrical 1,1′- or 1,2′-binaphthyl derivatives[4] as well as many symmetrical 2,2′-binaphthyl[5] or 2,2′-binaphthoquinone[6,7] derivatives belonging to a large class of natural products. A very limited number of unsymmetrical 2,2′-binaphthyl derivatives was reported,[4] but none of the methods which afforded them was convenient for our purpose,[8] and we were led to devise another approach based upon the aromatic $S_{RN}1$ reaction.

All the carbon atoms of the target molecules could indeed be assembled in a single step by an $S_{RN}1$(Ar) reaction between 2′-haloacetophenone and 2′-acetonaphthone to give the product P, a direct precursor of 2,2′-binaphthalene (Scheme I).

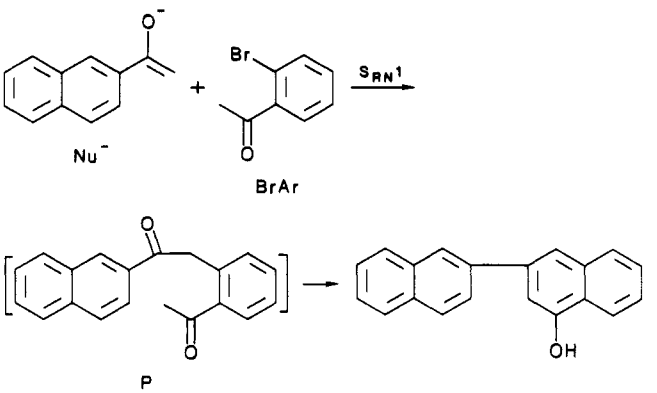
A large number of variously ortho functionalized aryl halides and series of ketone enolates are known to be compatible with the $S_{RN}1$ mechanism.[9] Concerning the acetyl group, earlier studies had shown that 2′-bromoacetophenone reacts well with sulfanions,[10a] and its reaction with ketone enolates has not been reported;[10b] acetone enolate however, reportedly does not react with the para isomer, 4′-bromoacetophenone.[10c] The suitability of the 2′-acetonaphthone-derived enolate to behave as a nucleophile in $S_{RN}1$ reactions was not documented either and accordingly we had to investigate the feasibility of $S_{RN}1$ reactions between 2′-bromoacetophenone and 2′-acetonaphthone and thereafter between variously substituted reactants.

A model reaction between 2′-acetonaphthone **1a** and the substrate **2a** carried out under standard $S_{RN}1$ conditions (liquid $NH_3$; −33 °C; photostimulation) gave directly the 2,2′-binaphthyl derivative **3a** (Table I, entry 1) resulting

**Scheme I**




**Scheme II**




$$BrAr \xrightarrow{e^-} [BrAr]^{\bullet -} \quad (1)$$

$$[BrAr]^{\bullet -} \rightarrow [Ar]^{\bullet} + Br^- \quad (2)$$

$$[Ar]^{\bullet} + Nu^- \rightarrow [P]^{\bullet -} \quad (3)$$

$$[P]^{\bullet -} + BrAr \rightarrow P + [BrAr]^{\bullet} \quad (4)$$

(1) Studies in $S_{RN}1$ Series. Part 19. Part 18: Beugelmans, R.; Bois-Choussy, M. *Tetrahedron*, in press.

(2) The subject has been reviewed recently: Sainsbury, M. *Tetrahedron Rep.* **1980**, *36* (98), 3327.

(3) The main general methods for biphenyl synthesis are based upon coupling of aryl halides with: (a) another aryl halide relatively inert (the Ullmann reaction and its modifications, reviewed by: Fanta, P. E. *Synthesis* **1974**, 9. Lindley, J. *Tetrahedron Rep. Tetrahedron* 1984, *40* (163), 1433. See also ref 2); (b) aryl zinc derivatives (Neghishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821); (c) aryl Grignard reagent (Widdowson, D. A.; Zhang, Y.-S. *Tetrahedron* **1986**, *42*, 2111). Recently, trapping of arynes by aryl Grignard reagents (Hart, H.; Harada, K.; Frank-Du, C.-J. *J. Org. Chem.* **1985**, *50*, 3104) and further modifications of the Ullmann reaction (Yamashita, J.; Inoue, Y.; Kondo, T.; Hashimoto, H. *Chem. Lett.* **1986**, 407) have been reported.

(4) The above reactions were also used for binaphthyl synthesis, which can also be achieved by reacting naphthyl Grignard reagents with 1- or 2-tetralones or by adding naphthols to naphthoquinones. For a recent and exhaustive review, see: Tisler, M. *Org. Prep. Proced. Int.* **1986**, *18*, 19.

(5) An interesting product possessing this skeleton is gossypol, a potential antifertility agent for males (Quian, S.-Z.; Wang, Z.-G. *Annu. Rev. Pharmacol. Toxicol.* **1984**, *24*, 329), which is intensively investigated (Meltzer, P. C.; Bickford, P. M.; Lambert, G. J. *J. Org. Chem.* **1985**, *50*, 3121. Venuti, M. C. *J. Org. Chem.* **1981**, *46*, 3124. Masciadri, R.; Angst, W.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1985**, 1573. Sampath, D. S.; Balaram, P. *J. Chem. Soc., Chem. Commun.* **1986**, 649).

(6) Thomson, R. H. *Naturally Occurring Quinones*; Academic: London, 1971.

(7) Laatsch, H. *Liebigs Ann. Chem.* **1985**, 1847 and references therein.

(8) A possible approach was found in a study about aromatization of some 3,4-octahydronaphtho-7,8-benzocoumarins (Chebaane, K.; Guyot, M. *Tetrahedron* **1977**, *32*, 757), the outcome of which are unsymmetrical 2,2′-binaphthyl derivatives (36–90%). The number of steps and the overall low yields dissuaded us from further investigations.

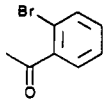
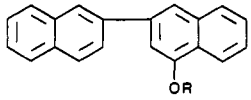
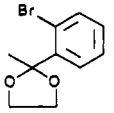
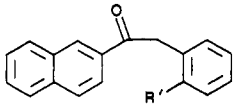
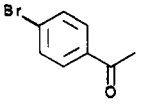
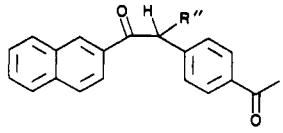
(9) Beugelmans, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 547.

(10) (a) Beugelmans, R.; Bois-Choussy, M.; Boudet, B. *Tetrahedron* **1983**, *39*, 4153. (b) Bunnett, J. F.; Michel, E.; Galli, C. *Tetrahedron* **1985**, *41*, 4119. (c) Bunnett, J. F.; Sundberg, J. E. *Chem. Pharm. Bull.* **1975**, *23*, 2620.

(11) Rossi, R. A.; de Rossi, R. H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*; ACS Monograph 178; American Chemical Society: Washington, DC, 1983.

0022-3263/87/1952-3880$01.50/0 

**Table I. Model Reactions between 2′-Acetonaphthone (1a) and Various Haloacetophenones 2**

| entry | substrate | solv | conditions[a] | products | yield,[b] % |
|---|---|---|---|---|---|
| |  | | |  | |
| | **2** | | | **3** | |
| 1 | **2a** | $NH_3$ | *c* | **3a**, R = H | 72 |
| 2 | **2a** | $NH_3$ | *d* | **3a**, R = H | 0 |
| 3 | **2a** | $NH_3$ | *c*, *e* | **3a**, R = H | 42 |
| 4 | **2a** | $Me_2SO$ | *c* | **3a**, R = H | 82 |
| 5 | **2a** | $Me_2SO$ | *d* | **3a**, R = H | 0 |
| 6 | **2a** | $Me_2SO$ | *c*, *e* | **3a**, R = H | 72 |
| 7 | **2a** | $Me_2SO$ | *c*, *f* | **3b**, R = *i*-$C_3H_7$ | 76 |
| |  | | |  | |
| 8 | **2b** | $Me_2SO$ | *c* | **4a**, R′ = $C[O(CH_2)_2O]CH_3$ | 0 |
| |  | | | | |
| 9 | **2c** | $Me_2SO$ | *c* | **4b**, R′ = H | 0 |
| |  | | |  | |
| | **2d** | | | | |
| 10 | **2d** | $NH_3$ | *c* | **5a**, R″ = H | 56 |
| 11 | **2d** | $Me_2SO$ | *c* | **5b**, R″ = $C_6H_4COCH_3$-*p* | 24 |
| | | | | **5a**, R″ = H | 54 |
| | | | | **5b**, R″ = $C_6H_4COCH_3$-*p* | 25 |
| |  | | | | |
| 12 | **2e** | $Me_2SO$ | *c* | **4b**, R′ = H | 49 |

[a] Reaction time, 90 min. [b] Yields for pure products after isolation. [c] Photostimulation by a Rayonet apparatus equipped with 8 RUL 3500 Lamps, filtered by Pyrex. [d] In the dark. [e] *m*-Dinitrobenzene, 0.2 equiv, calculated upon **2a**. [f] Br-*i*-$C_3H_7$ (8.5 mmol) added after irradiation in the reaction medium and heating at 80 °C for 20 min.

from the primary $S_{RN}1$ product P by way of an intramolecular aldol condensation under the basic conditions prevailing in the medium[12] (Scheme II).

Classical tests supporting the four-step $S_{RN}1$ chain mechanism[11,13] detailed in Scheme II are collected in Table I: (i) The reaction did not take place in the dark (entry 2) since, no activation energy being provided, no radical anion $[BrAr]^{\bullet-}$ was generated, and the reaction was not initiated (eq 1). (ii) The rate of the reaction was significantly reduced when *m*-dinitrobenzene (*m*-DNB) was added (entry 3) since the radical anions $[BrAr]^{\bullet-}$ or $[P]^{\bullet-}$ were oxidized in a termination step to give the stable $[m\text{-DNB}]^{\bullet-}$, which prevents the chain propagation (eq 2–4). Reacting **1a** and **2a** in dimethyl sulfoxide ($Me_2SO$), also known to be a good solvent,[14,15] gave **3a**, in slightly higher yield (entry 4). The fact that no reaction took place in the dark (entry 5) supports the $S_{RN}1$ mechanism in $Me_2SO$ too, in spite of the weak electron-trapping effect of *m*-DNB[16] (entry 6). As the product **3a** was obtained in either solvent, we have chosen the second one for synthetic purposes since the alkylation could be done in situ (the aldol condensation product issued from P allows alkylation by heating the mixture with Br-*i*-$C_3H_7$ to give **3b** after workup) to give the more conveniently handled ether derivative **3b** (entry 7).

An attempt to isolate the primary $S_{RN}1$ product was made by reacting the protected 2′-bromoacetophenone **2b** with **1a** (entry 8). No substitution product **4a** was formed, and the reactants were recovered unchanged under the conditions which had led to **3a**. The inertness of bromobenzene (entry 9) and the formation of **5a** (together with **5b**, which results from an $S_{RN}1$ reaction of the enolizable ketone **5a** which behaves as a nucleophile toward **2d**[1,17]) from 4′-bromoacetophenone and **1a** [entries 10 ($NH_3$) and 11 ($Me_2SO$)] also indicated that the electronic effect exerted by the free acetyl group was crucial for this $S_{RN}1$ reaction. As anticipated from the known relative leaving group efficiency of halogens in $S_{RN}1$ reactions (I > Br ≫ Cl), iodobenzene was found to afford **4b** when reacted with **1a** (entry 12), but the moderate yield of this experiment sharply contrasts with the higher yields of substitution products obtained from 2′- or 4′-bromoacetophenone in spite of their less reactive leaving group.

The unsymmetrical polyhydroxylated 2,2′-binaphthyl derivatives would be obtained if the results of Table I were extended to hydroxylated 2′-bromoacetophenone or to 2′-acetonaphthone. Therefore the next step of our study was reacting properly protected[13] di- or trihydroxy-2′-bromoacetophenone **2f** or **2g** with the simple 2′-acetonaphthalene **1a** derived enolate. Thus, 2,2′-binaphthalenes **3c** or **3d** tri- or tetrasubstituted on one naphthalene sub-

(12) A related intramolecular aldol reaction yielding 3-acetyl-2-methylindene has been reported by: Bunnett, J. F.; Singa, P. *J. Org. Chem.* **1981**, *46*, 5022.
(13) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(14) Scamehorn, R. G.; Bunnett, J. F. *J. Org. Chem.* **1979**, *44*, 2605.
(15) Scamehorn, R. G.; Hardacre, J. M.; Lukanich, J. M.; Sharp, L. R. *J. Org. Chem.* **1984**, *49*, 4881.
(16) Swartz, J. E.; Bunnett, J. F. *J. Org. Chem.* **1979**, *44*, 340.
(17) Similar $S_{RN}1$ substitution taking place on the primary $S_{RN}1$ products were reported: ref 1, 12.

**Table II. Preparation[a] of 2,2′-Binaphthalenes from 2′-Acetonaphthones 1a–c and 2′-Bromoacetophenones 2a,f,g**

| ketone (enolate) | | | substrate | | | | 2,2′-binaphthalene | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | | $R_3$ | $R_4$ | $R_5$ | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | yield,[b] % |
| **1a** | H | H | **2f** | H | $OCH_3$ | $OCH_3$ | **3c** | H | H | H | $OCH_3$ | $OCH_3$ | 80 |
| **1a** | H | H | **2g** | $OCH_3$ | $OCH_3$ | $OCH_3$ | **3d** | H | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | 52 |
| **1b** | H | $OCH_3$ | **2a** | H | H | H | **3e** | H | $OCH_3$ | H | H | H | 60 |
| **1c** | O-*i*-$C_3H_7$ | H | **2a** | H | H | H | **3f** | O-*i*-$C_3H_7$ | H | H | H | H | 83 |
| **1b** | H | $OCH_3$ | **2f** | H | $OCH_3$ | $OCH_3$ | **3g** | H | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | 59 |
| **1b** | H | $OCH_3$ | **2g** | $OCH_3$ | $OCH_3$ | $OCH_3$ | **3h** | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | $OCH_3$ | 73 |
| **1c** | O-*i*-$C_3H_7$ | H | **2f** | H | $OCH_3$ | $OCH_3$ | **3i** | O-*i*-$C_3H_7$ | H | H | $OCH_3$ | $OCH_3$ | 74 |
| **1c** | O-*i*-$C_3H_7$ | H | **2g** | $OCH_3$ | $OCH_3$ | $OCH_3$ | **3j** | O-*i*-$C_3H_7$ | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | 72 |

[a] (i) $S_{RN}1$ reaction in $Me_2SO$, irradiated until disappearance of substrate. (ii) Treatment in situ by Br-*i*-$C_3H_7$. [b] Yields for pure products after isolation.

unit only were obtained (Table II).

In order to get molecules unsymmetrically substituted on both naphthalene subunits, $S_{RN}1$ reactions had to be run between substituted 2′-bromoacetophenones and substituted 2′-acetonaphthone derived enolates. That such enolates could be nucleophiles suitable for $S_{RN}1$ reactions was first shown by reacting 2′-acetonaphthones substituted on position 1′ or 6′ by the electron-releasing group OR **1b** or **1c** with the simple 2′-bromoacetophenone **2a**; the expected 2,2′-binaphthyl derivatives **3e** or **3f** hydroxylated on both naphthalenic subunits were then obtained. More highly hydroxylated derivatives were prepared by combining differently the same building blocks, and thus reactions carried out between **1b** or **1c** and **2f** or **2g** afforded the tetrasubstituted or the pentasubstituted 2,2′-binaphthalene **3g**, **3h**, **3i**, or **3j**.

This study has shown new aspects of the $S_{RN}1$(Ar) reaction: (i) the compatibility and the electronic effect of the free acetyl group borne by the substrates; (ii) the property of the 2′-acetonaphthone-derived enolate to behave as a good nucleophile toward those substrates, which were combined to provide a new convergent one-pot synthetic route to unsymmetrically substituted 2,2′-binaphthalenes. (We have observed that 1′-acetonaphthone-derived enolate is also a good nucleophile toward **2a** and gave 1,2′-binaphthalenes. Those results will be reported separately.)

## Experimental Section

**General.** Melting points are uncorrected and were measured on a Reichert melting point apparatus. Boiling points were measured on a Büchi GKR-50 apparatus. Low-resolution mass spectra were obtained on an AEI MS50 spectrometer; $^1H$ NMR spectra (in $CDCl_3$) were recorded with Brüker WP-200-SY (200 MHz) instruments; chemical shifts from tetramethylsilane are given in δ. Purification were achieved by column chromatography (CC), by preparative thin-layer chromatography (PTLC), or by repeated crystallization.

**Starting Materials.** 2′-Acetonaphthone (**1a**), 6′-methoxy-2′-acetonaphthone (**1b**), 2′-bromoacetophenone (**2a**), bromobenzene (**2c**), 4′-acetophenone (**2d**), and iodobenzene (**2e**) are commercially available products.

**2-(2-Bromophenyl)-2-methyl-1,3-dioxolane (2b).** The treatment of 2′-bromoacetophenone with ethylene glycol and toluenesulfonic acid in anhydrous benzene with a Dean–Stark apparatus under reflux followed by classical workup and distillation afforded **2b**: bp 66 °C (0.17 mmHg) [lit.[18] bp 144 °C (15 mmHg)].

**1′-Isopropoxy-2′-acetonaphthone (1c).** 1′-Hydroxy-2′-acetonaphthone (71 mmol) dissolved in DMF (140 mL) was treated with $CO_3K_2$ (34 g) and 2-bromopropane (23 mL) at 80 °C for 2 h. Classical workup and purification (CC, silica gel, $CH_2Cl_2$; distillation) afforded **1c**: bp 130 °C (0.08 mmHg).

**2′-Bromo-4′,5′-dimethoxyacetophenone (2f).** A Grignard reaction of 2-bromo-4,5-dimethoxybenzaldehyde with methylmagnesium iodide and subsequent oxidation of the corresponding alcohol by $CrO_3$/3,5-dimethylpyrazole afforded **2f**: mp 74–76 °C (ethanol) (lit.[19] mp 74–76 °C).

**2′-Bromo-3′,4′,5′-trimethoxyacetophenone (2g).** Treating 3,4,5-trimethoxybenzaldehyde (10 mmol) with *N*-bromosuccinimide (10.2 mmol) in chloroform (20 mL) under reflux for 4 h gave 2-bromo-3,4,5-trimethoxybenzaldehyde, which was purified (CC, silica gel, $CH_2Cl_2$) and treated following the procedure used for **2f** to afford **2g**: mp 53–54 °C (methylene chloride/*n*-hexane) (lit.[20] mp 34.5–35 °C).

**General Procedure.** Into a 100-mL two-necked Pyrex tube containing distilled $Me_2SO$ (25 mL) were added under argon the ketone (4 mmol), sublimed *t*-$C_4H_9OK$ (4 mmol), and the substrate (1 mmol). Irradiation was performed in a Rayonet apparatus (S.O. New England Co) equipped with eight RUL 3500 lamps, and the course of the reaction was monitored by analyzing aliquots (TLC). After consumption of the substrate, 2-bromopropane (8.5 mmol) was added, and the solution was heated at 80 °C for 20 min. After cooling to 20 °C and water addition (150 mL), the solution was extracted with ethyl acetate (3 × 30 mL), and the organic fractions were washed with saturated water solution of sodium chloride (2 × 150 mL), dried over magnesium sulfate, and concentrated to afford crude product, purified by PTLC or repeated crystallization. Reactions in liquid ammonia (50 mL, condensed by dry ice) were run at −33 °C under argon; after treatment by $NH_4Cl$ and evaporation of $NH_3$ the products were extracted by ethyl acetate (3 × 30 mL).

**4-Hydroxy-2,2′-binaphthalene (3a)**: irradiation time, 90 min; purification by PTLC; mp 125 °C (methylene chloride/*n*-hexane); NMR δ 7.31 (d, 1 H), 7.54–7.70 (m, 4 H), 7.87 (s, 1 H), 7.88–8.08 (m, 5 H), 8.22 (d, 1 H), 8.30 (dd, 1 H); MS, *m/e* 270 ($M^+$).

**4-Isopropoxy-2,2′-binaphthalene (3b)**: irradiation time, 90 min; purification by PTLC; mp 89.0–90.5 °C (methylene-chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 4.93 (sept, 1 H), 7.27 (d, 1 H), 7.50–7.61 (m, 4 H), 7.76 (s, 1 H), 7.87–8.07 (m, 5 H), 8.16 (s, 1 H), 8.35 (dd, 1 H); MS, *m/e* 312 ($M^+$), 270. Anal. Calcd for $C_{23}H_{20}O$: C, 88.46; H, 6.41. Found: C, 88.20; H, 6.44.

**2-Phenyl-2′-acetonaphthone (4b)**: irradiation time, 90 min; purification by PTLC; mp 98.5–99.5 °C (methylene chloride/*n*-hexane) (lit.[21] mp 99–99.5 °C).

**2-(4-Acetylphenyl)-2′-acetonaphthone (5a)**: irradiation time, 90 min; purification by PTLC; mp 171.5–172 °C (methylene chloride/*n*-hexane; NMR δ 2.61 (s, 3 H), 4.54 (s, 2 H), 7.49 (d, 2 H), 7.60–7.73 (m, 2 H), 7.93–8.17 (m, 6 H), 8.63 (s, 1 H); MS, *m/e* 288 ($M^+$), 155, 127. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.33; H, 5.56. Found: C, 83.03; H, 5.48.

(18) Schiemenz, G. P.; Kaack, H. *Liebigs Ann. Chem.* **1973**, 1480.
(19) McDonald, E.; Smith, P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 837.
(20) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790.
(21) Ruggli, P.; Reinert, M. *Helv. Chim. Acta* **1926**, *9*, 67.

**2,2-Bis(4-acetylphenyl)-2′-acetonaphthone (5b)**: purification by PTLC; mp 139–141 °C (methylene chloride/*n*-hexane); NMR δ 2.58 (s, 6 H), 6.31 (s, 1 H), 7.43 (d, 4 H), 7.51–7.66 (m, 2 H), 7.83–8.05 (m, 8 H), 8.50 (s, 1 H); MS, *m/e* 406 ($M^+$), 208, 165, 155, 127.

**4-Isopropoxy-6,7-dimethoxy-2,2′-binaphthalene (3c)**: irradiation time, 105 min; purification by repeated crystallization from methylene chloride/methanol; mp 154–155.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 4.00 (s, 3 H), 4.04 (s, 3 H), 4.95 (sept, 1 H), 7.22 (d, 1 H), 7.27 (s, 1 H), 7.54–7.62 (m, 2 H), 7.63 (s, 1 H), 7.70 (s, 1 H), 7.93–8.07 (m, 4 H), 8.21 (s, 1 H); MS, *m/e* 372 ($M^+$), 330. Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.65; H, 6.45. Found: C, 80.56; H, 6.67.

**4-Isopropoxy-6,7,8-trimethoxy-2,2′-binaphthalene (3d)**: irradiation time, 120 min; purification by repeated recrystallization from methylene chloride/methanol; mp 97–99 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 3 H), 4.93 (sept, 1 H), 7.25 (d, 1 H), 7.47 (s, 1 H), 7.51–7.63 (m, 2 H), 7.91–8.04 (m, 5 H), 8.21 (s, 1 H); MS, *m/e* 402 ($M^+$), 360, 345. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.47. Found: C, 77.56; H, 6.48.

**4-Isopropoxy-6′-methoxy-2,2′-binaphthalene (3e)**: irradiation time, 75 min; purification by PTLC mp 143.5–144.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.98 (s, 1 H), 4.94 (sept, 1 H), 7.25–7.37 (m, 3 H), 7.48–7.65 (m, 2 H), 7.79 (s, 1 H), 7.89–8.01 (m, 4 H), 8.16 (s, 1 H), 8.41 (dd, 1 H); MS, *m/e* 342 ($M^+$), 300. Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.21; H, 6.43. Found: C, 84.11; H, 6.44.

**1,4′-Diisopropoxy-2,2′-binaphthalene (3f)**: irradiation time, 120 min; purification by PTLC; mp 31–35 °C; NMR δ 1.06 (d, 6 H), 1.50 (d, 6 H), 4.09 (sept, 1 H), 4.89 (sept, 1 H), 7.36 (s, 1 H), 7.51–7.78 (m, 7 H), 7.92 (dd, 2 H), 8.40 (dd, 2 H); MS, *m/e* 370 ($M^+$), 328, 286. Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.32; H, 7.03. Found: C, 84.08; H, 7.12.

**4-Isopropoxy-6,6′,7-trimethoxy-2,2′-binaphthalene (3g)**: irradiation time, 75 min; purification by repeated recrystallization from methylene chloride/methanol; mp 158–158.5 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.99 (s, 3 H), 4.06 (s, 3 H), 4.08 (s, 3 H), 4.92 (sept, 1 H), 7.19 (s, 1 H), 7.21–7.30 (m, 3 H), 7.63 (s, 1 H), 7.66 (s, 1 H), 7.85–7.97 (m, 3 H), 8.12 (s, 1 H); MS, *m/e* 402 ($M^+$), 360. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.61; H, 6.47. Found: C, 77.42; H, 6.68.

**4-Isopropoxy-6,6′,7,8-tetramethoxy-2,2′-binaphthalene (3h)**: irradiation time, 100 min; purification by repeated recrystallization from methylene chloride/methanol; mp 149–150 °C (methylene chloride/*n*-hexane); NMR δ 1.53 (d, 6 H), 3.97 (s, 3 H), 4.03 (s, 3 H), 4.07 (s, 3 H), 4.13 (s, 3 H), 4.90 (sept, 1 H), 7.19–7.28 (m, 3 H), 7.45 (s, 1 H), 7.85–7.93 (m, 3 H), 8.00 (s, 1 H), 8.14 (s, 1 H); MS, *m/e* 432 ($M^+$), 390, 375. Anal. Calcd for $C_{27}H_{28}O_5$: C, 75.00; H, 6.48. Found: C, 74.78; H, 6.58.

**1′,4-Diisopropoxy-6,7-dimethoxy-2,2′-binaphthalene (3i)**: irradiation time, 45 min; purification by PTLC; mp 71–73 °C (methanol/water); NMR δ 1.06 (d, 6 H), 1.49 (d, 6 H), 4.04 (s, 3 H), 4.08 (s, 3 H), 4.09 (sept, 1 H), 4.88 (sept, 1 H), 7.22 (s, 1 H), 7.27 (s, 1 H), 7.53–7.77 (m, 6 H), 7.92 (dd, 1 H), 8.40 (dd, 1 H); MS, *m/e* 430 ($M^+$), 388, 346, 345. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.14; H, 6.98. Found: C, 77.98; H, 6.85.

**1′,4-Diisopropoxy-6,7,8-trimethoxy-2,2′-binaphthalene (3j)**: irradiation time, 75 min; purification by PTLC; mp 51–53 °C (methanol/water); NMR δ 1.08 (d, 6 H), 1.50 (d, 6 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 4.08 (sept, 1 H), 4.11 (s, 3 H), 4.88 (sept, 1 H), 7.35 (d, 1 H), 7.48 (s, 1 H), 7.53–7.78 (m, 4 H), 7.90–7.95 (m, 2 H), 8.40 (dd, 1 H); MS, *m/e* 460 ($M^+$), 418, 376, 375, 344. Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.65; H, 6.96. Found: C, 75.90; H, 7.11.

**Registry No.** **1a**, 93-08-3; **1b**, 3900-45-6; **1c**, 109124-52-9; **2a**, 2142-69-0; **2b**, 50777-64-5; **2d**, 99-90-1; **2e**, 591-50-4; **2f**, 74746-10-4; **2g**, 73252-59-2; **3a**, 109124-60-9; **3b**, 109124-61-0; **3c**, 109124-53-0; **3d**, 109124-54-1; **3e**, 109150-64-3; **3f**, 109124-55-2; **3g**, 109124-56-3; **3h**, 109124-57-4; **3i**, 109124-58-5; **3j**, 109124-59-6; **4b**, 1762-15-8; **5a**, 109124-62-1; **5b**, 109124-63-2; 1′-hydroxy-2′-acetonaphthone, 711-79-5; 2-bromo-4,5-dimethoxybenzaldehyde, 5392-10-9; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 2-bromo-3,4,5-trimethoxybenzaldehyde, 35274-53-4.

# Stereoselective Total Synthesis of (±)-Aristolactone and (±)-Epiaristolactone via [2,3] Wittig Ring Contraction

James A. Marshall,* Jacques Lebreton, Bradley S. DeHoff, and Todd M. Jenson

*Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208*

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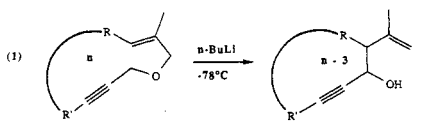
The germacranolide bridged lactone aristolactone (**16**) has been synthesized starting from geranyl acetate. Homologation of the derived chloride **5** via coupling with [(triisopropylsilyl)propargyl]magnesium bromide followed by deprotection, metalation, and addition of formaldehyde gave the chloro alcohol **9**. This was smoothly cyclized by treatment with ethylmagnesium bromide in THF–HMPA. The resulting 13-membered allylic propargylic ether **10** underwent facile [2,3] Wittig rearrangement to the cyclodecenyne **11** with trans-related vicinal OH and isopropenyl groupings. Mitsunobu inversion of this propargylic alcohol with benzoic acid followed by ester cleavage yielded the cis isomer **13**. Hydroalanation of the alkyne with Red-Al and trapping of the resulting alanate with *N*-iodosuccinimide afforded the unstable vinyl iodide **14**. Carbonylation over $Pd(Ph_3P)_4$ gave (±)-aristolactone. A more direct route to the cis alcohol **13** via [2,3] Wittig rearrangement of the macrocyclic *Z*-allylic propargylic ether **33** was also effected.

Pursuant to studies on the synthesis of medium-ring and macrocyclic natural products we developed a novel variant of the [2,3] Wittig rearrangement whereby cyclic allylic propargylic ethers were found to undergo a remarkably facile ring contraction to cycloalkynols.[1,2] In our initial application of this methodology to cembranoid natural products ($n$ = 17), we were able to control the stereoselectivity of the rearrangement by changing the solvent from hexane–THF (trans product) to THF–HMPA (cis product).[1a,3] The cycloalkynol products proved well suited to

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(2) Takehashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

(3) Abbreviations: DEAD = diethyl azodicarboxylate; DIBAH = diisobutylaluminum hydride; DMAP = 4-(dimethylamino)pyridine; HMPA = hexamethylphosphoric triamide; KHMDS = potassium hexamethyldisilazide, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride; TBAF = tetra-*n*-butylammonium fluoride; TBHP = *tert*-butyl hydroperoxide; THF = tetrahydrofuran; TIPS = triisopropylsilyl; TLC = thin layer chromatography.

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