A Fully Synthetic Route to the Neurotrophic Illicinones by Sequential Aromatic Claisen Rearrangements

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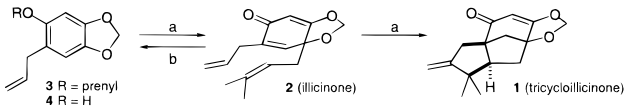
Fukuyama and colleagues have rcently reported the isolation of tricycloillicinone (**1**) from *Illicium tashiroi*.[1] Illicinone, **2**, also obtained from *Illicium tashiroi*, might be a biosynthetic precursor of **1**. Indeed, in an earlier investigation, photolysis of **2** had been shown to afford **1**.[2] Interestingly, compound **2** and its photo product **1** were available from photolysis of **3**,[3] the prenylation product of **4**. Compound **4** itself is obtained from the pyrolysis of **2** (Scheme 1).

The illicinones are members of an intriguing class of "small molecule" neurotrophic factors. Fukuyama has shown that such compounds exhibit their effects through increased choline acetyltransferase (ChAT) activity,[4] resulting in the enhanced sprouting during the development of neurons in a primary culture of fetal rat cerebral tissues.[5] Small molecule neurotrophic factors could conceivably be of at least palliative value in Alzheimer's disease, which is characterized by markedly reduced ChAT function.[6]

To implement our proposed strategy effectively, it was necessary to accomplish, with conciseness, the synthesis of substrates for aromatic Claisen rearrangements and to control the rearrangement step itself in the context of extensively oxygenated matrixes.[7,8] For instance, a direct synthesis of **5** from methylenedioxyresorcinol is complicated by a lack of control in either phenolic allylation or silyl protection.[9] As will be seen, we solved this problem through the use of a carbomethoxy group as a surrogate for the hydroxy residue following the precedent of Boger and Coleman (see sequence starting with **12**).[10]

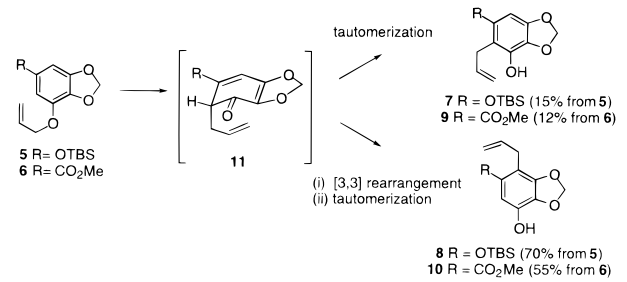
Furthermore, the principal rearrangement products of **5** and **6** were the para products **8** and **10**, rather than the desired ortho isomers **7** and **9** (Scheme 2). The tendency for the formation of para-Claisen products in such systems is well precedented.[7] Seemingly, **8** and **10** are produced from Cope rearrangement of **11**, the presumed intermediate in the ortho route. Remarkably, the Cope step is apparently competitive with simple tautomerization of **11**, which would have given **7** or **9**.[11]

Scheme 1. Interconversions in the Illicinone Series[a]

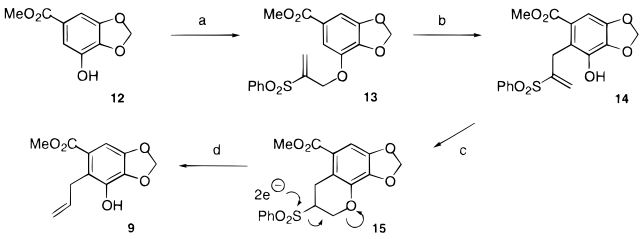


[a] (a) 450 W Hg lamp, 30 min., **3** → **2** (7%) + **1** (5%) or **2** → **1** (28%); (b) 200 °C, 4 h, **2** → **4** (50%).

Scheme 2



Scheme 3[a]



[a] (a) $PhSO_2CH(CH_2Br)_2$, K_2CO_3, acetone, rt, 85%; (b) neat, 165 °C, 12 h, 94%; (c) K_2CO_3, acetone, Δ, >95%; (d) 10% Na−Hg, MeOH−EtOAc, −20 °C, 87%.

We wondered about the consequences of placing a group at C_2 of the allyl function, with respect to the ortho:para ratio in the Claisen rearrangement. In this connection, we synthesized compound **13** by alkylation of **12** with 1,3-dibromo-2-phenylsulfonylpropane as shown.[12,13] Thermolysis of **13**, neat, at temperatures as low as even 165 °C, gave Claisen rearrangement. Interestingly, the only isomer observed under these thermal conditions was the ortho product, **14** (94% yield). Following considerable difficulties in unveiling the allyl group of the desired **9** through attempted reductive cleavage of the sulfone function in **14**, an additional modification was introduced. When the Claisen rearrangement was conducted in the presence of potassium 2,6-dimethylphenoxide, a 94% yield of the benzopyran **15**, was obtained.[14] Presumably, under these conditions, compound **15** arises from base-induced Michael type cyclization of previously isolated **14**. Indeed, such a cyclization was independently achieved on isolated thermolysis product **14** through the action of potassium carbonate. Exposure of **15** to the action of sodium mercury amalgam produced **9** in 86% yield[15] (Scheme 3). Thus, Michael

(1) Fukuyama, Y.; Shida, N.; Kodama, M.; Chaki, H.; Yugami, T. *Chem. Pharm. Bull*. **1995**, *43*, 2270.

(2) Yakushijin, K.; Sekikawa, J.; Suzuki, R.; Morishita, T.; Furukawa, H.; Murata, H. *Chem. Pharm. Bull.* **1980**, *28*, 1951.

(3) Yakushijin, K.; Furukawa, H.; McPhail, A. T. *Chem. Pharm. Bull*. **1984**, *32*, 23. A tetracyclic structure (ring closure instead of H abstraction) is produced along with tricycloillicinone in 21%, see compound **6** in this citation.

(4) Delivery of exogenous protein factors to the CNS remains one of the major obstacles for trophic factor therapy. The discovery of cell permeable small trophic molecules represents a potential frontier in research directed at neurodegenerative diseases. Rosenburg, S. Section I: CNS Reagents. *Annual Reports in Medicinal Chemistry-27*; Academic Press: New York; 1992, p 41.

(5) Furukawa, H.; Shida, N.; Kodama, M. *Planta Med*. **1993**, *59*, 181.

(6) Hefti, F. *J. Neurobiol*. **1994**, *25*, 1418.

(7) Rhoads, S. J.; Raulins, N. R. *Organic Reactions*; John Wiley & Sons: New York, 1975; Vol. 22, p 1.

(8) The consecutive rearrangement strategy practiced here uses the same aromatic hydroxyl to direct rearrangements to the two flanking ortho centers. This is to be distinguished from the concept of tandem rearrangements; see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(9) (a) Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem*. **1983**, *48*, 1941. (b) Schneider, G. E.; Stevenson, R. *J. Org. Chem*. **1981**, *46*, 2969. (c) McKittrick, B. A.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 709.

(10) Boger, D.; Coleman, R. S. *J. Org. Chem*. **1986**, *51*, 5436.

(11) The ortho products do not rearrange to the para isomers. Seemingly, therefore, the para:ortho ratios are under kinetic control.

(12) Compound **12** was prepared as previously reported in one step from methyl gallate, see: Keserü, G. M.; Nógrádi, M.; Kajtár-Peredy, M. *Liebigs Ann. Chem*. **1994**, 361; cf. Kuo, G.-H.; Eissenstat, M. A. *Tetrahedron Lett*. **1997**, *38*, 3343.

(13) For the preparation of 1,3-dibromo-phenylsulfonylpropane, see: (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett*. **1985**, *26*, 425. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett*. **1985**, *26*, 4455.

(14) For a previous example of the conduct of a Claisen rearrangement in the presence of base, see: Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc*. **1977**, *99*, 4835.

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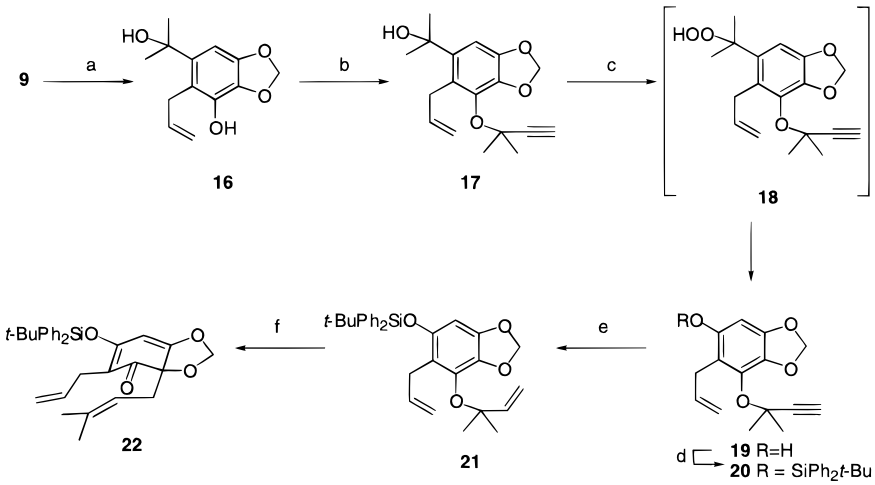
Scheme 4[a]



[a] (a) 4 equiv 1.4 M [MeLi−LiBr], THF, 12 h, 90%; (b) $(CH_3)_2C(Cl)CCH$, Kl, K_2CO_3, acetone, 60 °C, 48 h, 73%; (c) 50% H_2O_2:H_2SO_4 (5:4), CH_2Cl_2, 10 min, 60−85%; (d) TBDPSCl, imidazole, DMAP, CH_2Cl_2, >97%; (e) 10 mol% Pd−$CaCo_3$ (Pb-poisoned), quinoline, EtOAc, >95%; (f) toluene, 100 °C, 2 h, >95%.

like cyclization followed by reductive ring opening under conditions where Cope rearrangement or re-cyclization does not occur, was used to produce **9** with positional control.

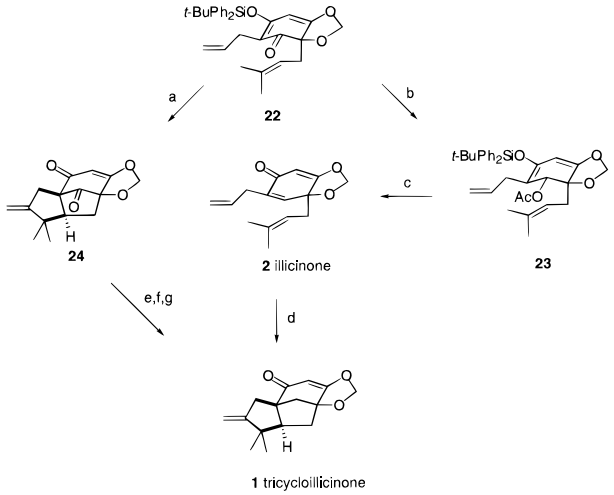
With this seemingly minor, but actually serious problem solved, we could direct our attentions to the second Claisen step. Once again, experience constrained us to follow a narrow pathway. Addition of excess methyllithium to **9** produced **16**. The latter could be alkylated with 3-chloro-3-methyl-1-butyne under catalysis with KI, giving rise to an 87% yield of **17**.[16] Subjection of this compound, at 0 °C, to the action of a mixture of hydrogen peroxide and sulfuric acid (5:4) produced **19**. The latter, upon silylation, provided **20**. We presume that the oxidative fragmentation of **17**, anticipated by the Boger−Coleman precedent,[10] arises from an exchange process leading to the formation, in situ, of the cumyl hydroperoxide, **18**. Criegee-like rearrangement of the latter provided **19**. Lindlar reduction of **20** afforded **21** which underwent smooth rearrangement at 100 °C in toluene to produce **22**[17] (Scheme 4).

Compound **22**, which is essentially an oxidized version of illicinone, serves as a general intermediate for reaching a variety of compounds in this series. For instance, treatment of **22** with L-Selectride, followed by acetylation and β-elimination provided **2** itself. Photolysis of illicinone, indeed, produced tricycloillicinone (**1**) as previously described.[3] In our hands thus far, however, this reaction occurs in only 10−15% yields.

Of greater value is the fact that heating of compound **22** with manganese(III) and copper(II) acetates, smoothly gave rise to **24**. Presumably during this reaction, the silyl enol ether was cleaved. The resultant β-diketone (which corresponds electronically to a vinylogous β-ketoester) then undergoes oxidative cyclization in the fashion developed by Corey and Snider.[18] Selective reduction of the ketone at the C_1 bridge and deoxygenation of the resultant alcohol as shown, led to **1**. In addition to producing the natural product in a more pleasing fashion, this route provides access to a wealth of analogue structures (Scheme 5).

At the chemical level our route to these small molecule neurotrophic agents illustrates a method to control the distribution of ortho to para Claisen rearrangement products in complex oxygenated systems in favor of the former (see compound **9**). The cumyl hydroperoxide rearrangement reaction simplified the otherwise difficult problems associated with differentiation of multiple oxygen functions in reaching pre-Claisen precursor **21**. Finally, application of the Snider reaction (**22** → **24**) provides a direct route to tricycloillicinone.

Scheme 5[a]



[a] (a) 2 equiv $Mn(OAc)_3 \cdot H_2O$, 1 equiv $Cu(OAc)_2 \cdot H_2O$, HOAc, 50 °C, 3 h, 70−80%; (b) i. L-Selectride, THF; ii. Ac_2O, DMAP, 82% overall; (c) neat DBU, rt, 1 h, 65%; (d) degassed Et_2O, 450 W Hg lamp, pyrex tube, 1 h, 10−15% (see ref 3); (e) LiAlH(O-*t*-Bu)$_3$, THF, 78%; (f) KHMDS, THF, −78 °C, then salt of DAMP and PhOC(S)Cl, −20 °C, overnight, 90%; (g) Bu_3SnH, AlBN, benzene, Δ, overnight, 42%.

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Supporting Information Available: Experimental procedures for compounds (**1**, **2**, **9**, **13**, **14**, **15**, **16**, **17**, **19**, **20**, **21**, **22**, **23**, **24**) are provided (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(15) Cf.: Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkins Trans. I* **1978**, 829.
(16) Hennion, G. F.; Sheehan, J. J.; Maloney, D. E. *J. Am. Chem. Soc.* **1950**, *72*, 3542 and references therein.
(17) Cf. Murray, R. D. H.; Sutcliffe, M. *Tetrahedron* **1975**, *31*, 2966.
(18) Cf. (a) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384. (b) Snider, B. B. *Chem Rev.* **1996**, *93*, 339. (c) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (d) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544. (e) Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.