A Fully Synthetic Route to the Neurotrophic Illicinones: Syntheses of Tricycloillicinone and Bicycloillicinone Aldehyde

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Abstract: Tricycloillicinone (**1**) and bicycloillicinone asaronacetal (**2**) were both isolated from extracts of the wood of *Illicium tashiroi*. These compounds were found to enhance the action of choline acetyltransferase, which catalyzes the synthesis of acetylcholine from its precursor. Since one of the characteristic symptoms of Alzheimer's disease involves degeneration of cholinergic neurons, resulting in markedly reduced levels of acetylcholine, compounds with the properties of **1** or **2** could well serve as agents in the treatment of such disorders. In this paper, we report the total synthesis of **1** and the construction of the core structure **3** of **2**. The tricycloillicinone synthesis employed a novel strategy to control the regiochemistry of two ortho Claisen rearrangements. A sulfonyl group introduced at C_2 of an allyl group effectively suppressed its unwanted rearrangement to the para position (**23** → **24**). Subsequently, ortho Claisen rearrangement was conducted using a reverse O-prenylated derivative **31** to furnish the desired **32**, selectively. **32** was used as a common precursor for the syntheses of both **1** and **3**. The application of Corey−Snider oxidative cyclization and the Barton−McCombie deoxygenation provided a direct route to **1**. For bicycloillicinone aldehyde **3**, a new tandem reaction using the Et_2AlCN to construct the cage structure (**39** → **41**) was employed. Flexible syntheses of the polycyclic illicinones should provide access to analogous structures for future biological and SAR studies.

Introduction

In 1995, Fukuyama and colleagues isolated tricycloillicinone from the toxic plant *Illicium tachiroi*, collected on Ishigaki island in Japan.[1,2] They determined its chemical structure to be that shown as structure **1**, mainly by extensive NMR analysis (Figure 1). Two years later, they reported the isolation of bicycloillicinone asaronacetal (**2**) from the same plant. The entire structure of **2** was elucidated through heavy reliance on spectroscopic analysis and chemical degradation. Not surprisingly, acid hydrolysis of **2** led to aldehyde **3**, in addition to the catechol portion. This finding confirmed the presence of the acetal moiety.

The highly compact arrangement of the polycyclic structures of **1**−**3** and the presence of the methylenedioxy function in a nonaromatic setting served to pose interesting challenges to the science of chemical synthesis. In the case of **2**, the complexity of the problem rises further, since provision must be arranged for an additional formyl carbon at C_3 in the form of a rare catechol-derived acetal. Perhaps an equally compelling factor in attracting our attention to the construction of these targets is that they were found to be inducers of choline acetyltransferase (ChAT). ChAT is responsible for the biosynthesis of the neurotransmitter acetylcholine, which has been identified as a bioregulator for cholinergic neuron function. Compounds **1** and **2** were reported to increase ChAT activity at 30 μM.[1−3] Since the dementia associated with neurodegenerative diseases has been partially attributed to atrophy of cholinergic neurons and corresponding deficiencies in acetylcholine levels, a search for chemical substances that could boost Ach levels at the locus of cholinergic neurons has continued for more than a decade.[4,5]

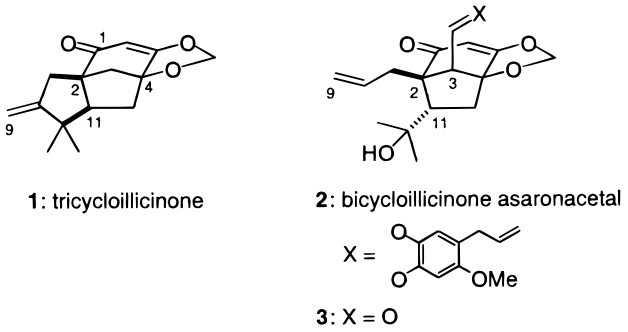

Figure 1. Structures of tricycloillicinone (**1**) and bicycloillicinone asaronacetal (**2**).

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

(2) Fukuyama, Y.; Hata, Y.; Kodama, M. *Planta Med.* **1997**, *63*, 275.

(3) Hatanaka, H.; Tsukui, H.; Nihonmatsu, I. *Dev. Brain Res.* **1988**, *39*, 85.

(4) (a) Hefti, F. *J. Neurobiol.* **1994**, 1418. (b) Hefti, F. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 239.

(5) The cholinesterase inhibitors such as denepezil (Aricept) and tacrine (Cognex), which are capable of increasing Ach levels, are now in use as Alzheimer's disease therapeutics. For a recent review, see: Giacobini, E. *Neurochem. Int.* **1998**, *32*, 413. We thank the reviewers for calling these agents to our attention.

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Several proteinoid factors such as nerve growth factor (NGF) have been found, and their potential roles in the development of the mature nervous system and in preventing neuronal degeneration have been suggested.[6] However, such proteins have expectedly poor pharmacokinetic characteristics and they fail to cross through the blood−brain barrier. This situation prevents their systemic application for treatment of central neurodegenerative diseases.[7] Accordingly, non-peptide small molecules, which are capable of increasing neurotransmitter biosynthesis and possibly supporting the survival of cholinergic neurons, attract considerable interest. Not surprisingly, the few non-peptide small molecules that manifest apparent activity in this challenge draw considerable notice.[8]

Furthermore, two FDA-approved Alzheimer therapeutics (Aricept and Coganex) apparently increase acetylcholine levels in the brain.[8e]

Considering the biological activity and the intriguing structures of the neurotrophic illicinones, we undertook a program directed to their total synthesis. In this paper, we report (i) the total synthesis of tricycloillicinone (**1**) and (ii) the synthesis of the aldehyde version **3** of bicycloillicinone asaronacetal (**2**). In the course of this synthetic journey, we solved a problem that arose in the context of conducting sequential aromatic Claisen rearrangements. The method employed is apt to be pertinent to other instances of bond reorganization reactions.

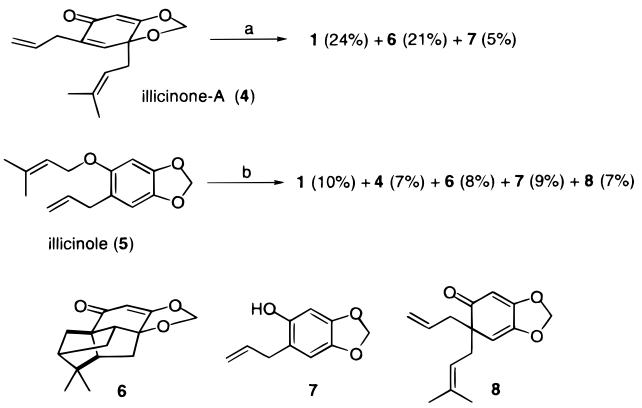
Synthetic Plan for Tricycloillicinone

Although **1** was isolated in 1995 from *I. tachiroi*, the compound had actually been generated earlier, through inadvertence, by Furukawa in 1984. In the course of searching for biologically active natural products, Japanese workers determined, in 1980, the structures of four novel phytoquinoids,[9] illicinones-A−D, from *I. tashiroi*.

The information, which was of the greatest value for our project, came from subsequent chemical investigations of illicinone-A (**4**, Scheme 1).[10] Irradiation of **4** with a mercury lamp for 1 h was claimed to afford compounds **1**, **6**, and **7** in 24%, 21%, and 5% yield, respectively. Additionally, reaction of illicinole (**5**) under the same conditions for 30 min furnished **1**, **4**, **6**, **7,** and **8** in low yields. The structure of **1**, isolated from these reactions, was unambiguously established by a single-crystal X-ray analysis. Thus, in 1995, **1** was reintroduced to the chemical community by Fukuyama et al. as tricycloillicinone, in the context of his natural product isolation exercise.[1] The earlier studies of Furukawa suggest **5** or **4** to be plausible intermediates in the biosynthesis of tricycloillicinone.

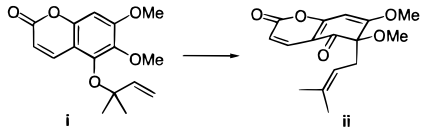
On basis of the above-described disclosure, we could in principle reach tricycloillicinone through preparation of illicinole (**5**) or illicinone-A. However, we were interested in a more logical, flexible, and chemically satisfying solution to gain access to this unusual skeleton. Such a systematic synthesis might provide a sound strategy to reach more complex neurotrophic illicinones such as **2**. The most challenging synthetic problem in synthesizing this molecular class appeared to be that of construction of the cagelike ring system. The results of Furukawa[10] suggested that the tricyclic structure of **1** could perhaps be constructed via the formation of a radical at C_2 of **4**. Given that irradiation-induced cyclization was inefficient for a selective synthesis, an alternative approach to generate the radical might prove to be more effective. Accordingly, we decided to apply an oxidative radical reaction of 1,3-dicarbonyl compounds using manganese(III). Such chemistry had been introduced by Corey and subsequently expanded by Snider for the construction of polycyclic systems (Scheme 2: **10** → **9**).[11] In principle, the initial loss of the C_2 hydrogen by oxidation would give a radical intermediate **11**. Sequential cyclizations could lead to **12**. Oxidation of this radical, associated with elimination of a hydrogen atom from C_8, would afford 3-oxytricycloillicinone (**9**). It was anticipated that this radical method could selectively construct the desired tricyclic system without undue complications of the other possible radical pathways. Four-electron reductive deoxygenation of **9** from C_3 would afford the target **1**. Importantly, the oxygen functionality of **9** at C_3 could serve as a conduit to synthesize analogues for further biological study.

Scheme 1.[a] Photochemical Reaction of the Illicinone Series



[a] Reagents and conditions: (a) Et_2O, 400-W mercury lamp, 20−30 °C, 1 h; (b) Et_2O, 400-W mercury lamp, 20−30 °C, 30 min.

Compound **10** would be prepared by ortho Claisen rearrangement of the reverse O-prenylated phenol **13**. Although we could not predict, a priori, the selectivity of the rearrangement, one literature example encouraged us to examine the possibilities inherent in such a dearomatization reaction.[12] Moreover, we expected that the sterically demanding nature of the dimethyl group on C_{12} might prevent the prenyl group in **10** from undergoing para rearrangement to C_6. The allyl group in **13** itself could be constructed by ortho Claisen rearrangement of



(6) Seiger, A.; Nordberg, A.; vonHolst, H.; Backman, L.; Ebendal, L.; Alafuzoff, I.; Ambria, K.; Herlitz, A.; Lilja, A. *Behav. Brain Res*. **1993**, *57*, 255.

(7) Resenburg, S. In *Annual Reports in Medicinal Chemistry*; Academic Press: New York; 1992; Vol. 27, p 41.

(8) cf. Isodunnianin: (a) Fukuyama, Y. Shida, N.; Kodama, M. *Planta Med.* **1993**, *59*, 181. Garsubellin A: (b) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm Bull*. **1997**, *45*, 947. Synthetic studies on garsubellin A: (c) Nicolaou K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc*. **1999**, *121*, 4724. K-252a derivatives: (d) Kaneko, M.; Saito, Y.; Saito, H.; Matsumoto, T.; Matsuda, Y.; Vaught, J. L.; Dionne, C. A.; Angeles, T. S.; Glicksman, M. A.; Neff, N. T.; Rotella, D. P.; Kauer, J. C.; Mallamo, J. P.; Hudkins, R. L. Murakata, C. *J. Med. Chem.* **1997**, *40*, 1863.

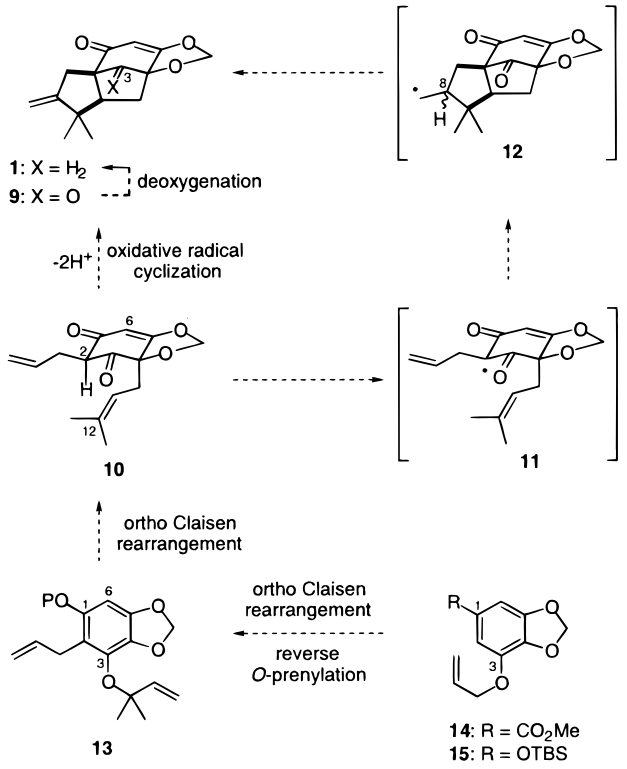
(9) Yakushijin, K.; Sekikawa, J.; Suzuki, R.; Morishita, T.; Furukawa, H.; Murata, H. *Chem. Pharm. Bull*. **1980**, *28*, 1951.

(10) Yakushijin, K.; Furukawa, H.; McPhail, A. T. *Chem. Pharm. Bull*. **1984**, *32*, 23.

(11) (a) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc*. **1984**, *106*, 5384. (b) Snider, B. B. *Chem. Rev*. **1996**, *96*, 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. For a review, see: (f) Snider, B. B. *Chem. Rev*. **1996**, *96*, 339.

(12) Murray et al. showed that coumarin derivative **i** underwent facile ortho Claisen rearrangement in the course of their extensive studies on coumarin-type natural products: Murray, R. D. H.; Sutcliffe, M.; M. Hasegawa. *Tetrahedron* **1975**, *31*, 2966.

Scheme 2. Synthetic Strategy en Route to Tricycloillicinone (**1**)

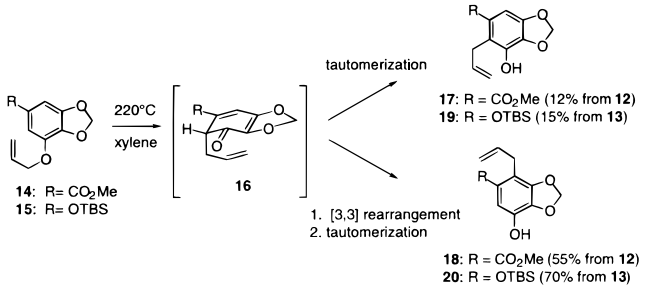


either **14** or **15**. It was envisioned that utilization of the same hydroxyl group for the two consecutive Claisen rearrangements would simplify the protecting group strategy required to build the highly oxygenated precursor **9**.[13] However, it was recognized that differentiation of phenolic hydroxyl functions in aromatic compounds is not always a small matter.[14] For instance, the synthesis of **15** from methylenedioxyresorcinol could be complicated by a lack of control in either the phenolic allylation or silyl protection steps. Thus, following the elegant precedents of Boger and Coleman,[15] we decided to use a carbonyl group as a surrogate for the hydroxy residue at C_1. The methyl ester in **14** could be converted to a tertiary alcohol at an appropriate stage in the synthesis. Given such an alcohol, benzylic hydroperoxide rearrangement could be exploited to deliver the required phenol at C_1 (see **13**).

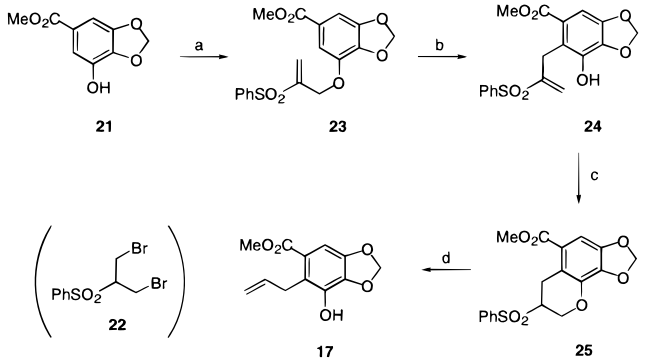
Total Synthesis of Tricycloillicinone[16]

To test the feasibility of the first ortho Claisen rearrangement, we prepared allyl ether **14** (Scheme 3). However, thermolysis of **14** provided the undesired rearrangement product **18** as the major product. The tendency for formation of para Claisen products in such systems is well precedented.[17] Mechanistically, Claisen rearrangement of **14** would lead to intermediate **16**

Scheme 3. First Attempts for Ortho Claisen Rearrangement



Scheme 4.[a] Regioselective Ortho Claisen Rearrangement



[a] Reagents and conditions: (a) **22**, K_2CO_3, acetone, room temperature, 85%; (b) toluene, 165 °C, 12 h; (c) K_2CO_3, acetone, reflux, 94% (two steps); (d) 10% Na−Hg, MeOH−EtOAc, −20 °C, 87%.

which could, in turn, could give rise either to **17** or to **18** (via subsequent Cope rearrangement followed by tautomerization). An independent experiment excluded the possibility of subsequent conversion of **17** to **18** under reaction conditions and suggested that the para/ortho ratio was under kinetic control. Apparently, the tautomerization of **16** is slower than the second sigmatropic rearrangement. Of course, in offering this analysis, we have not considered the possibility of a "direct" para Claisen rearrangement, which would not involve ortho Claisen intermediates.

We also investigated the case of substrate **15** with an electron-donating group at the C_1 position (see **15**). The reaction course did not change, though a slight yield improvement was observed. Due to the encountered complexities, we wondered about the consequences of placing a group at C_2 of the migrating allyl moiety to improve the ortho/para ratio of the rearrangement. It was hoped that such a group would suppress the migratory aptitude of the allyl function with respect to the presumed Cope phase of the tandem sequence discussed above. To apply this concept in the context of the total synthesis, this group would need to be introduced and removed both easily and selectively. With this consideration in mind, we chose a phenylsulfonyl group as a candidate substructure (Scheme 4). Alkylating agent **22** was prepared from allyl phenyl sulfide in two steps using a known procedure.[18] Base-induced combination of **21**[19] and **22** gave rise to the α,β-unsaturated sulfone **23** in 87% yield. Presumably, under these conditions, HBr is eliminated from **22**

(13) 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.

(14) cf. (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.

(15) (a) Boger, D.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 5436. For recent examples of this concept, see: (b) Boger, D.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717. (c) Sánchez, A. J.; Konopelski, J. P. *J. Org. Chem.* **1994**, *59*, 5445.

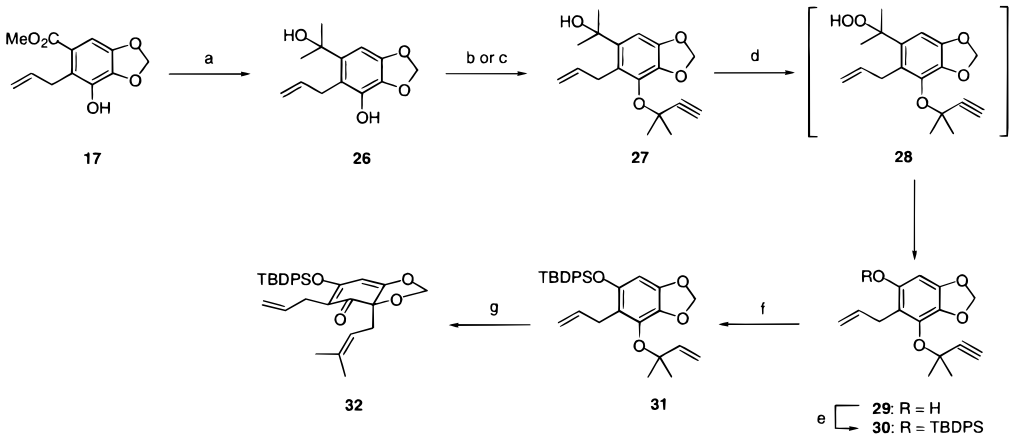
(16) For a preliminary account of this work, see: Pettus, T. R. R.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12684.

(17) Rhoads, S. J.; Raulins, N. R. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, London, Sydney, Toronto; 1975; Vol. 22, p 1.

(18) For the preparation of 1,3-dibromo-2-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.

(19) Compound **21** was prepared as previously reported in one step from commercially available methyl gallate; see: (a) Keserü, G. M.; Nógrádi, M.; Kajtár-Peredy, M. *Liebigs Ann. Chem.* **1994**, 361. (b) Kuo, G.-H.; Eissenstat, M. A. *Tetrahedron Lett.* **1997**, *38*, 3343.

Scheme 5[a]



[a] Reagents and conditions: (a) MeLi, THF, −78 °C to room temperature, 12 h, 90%; (b) $(CH_3)_2C(Cl)C{\equiv}CH$, KI, K_2CO_3, CH_3COCH_3, 60 °C, 48 h, 50−73%; (c) $(CH_3)_2C(OH)C{\equiv}CH$, $(CF_3CO)_2O$, DBU, then **26**, $CuCl_2{\cdot}H_2O$, DBU, room temperature, 12 h, 77% based on starting material (89% conversion); (d) 50% $H_2O_2-H_2SO_4$ (5:4), CH_2Cl_2, 0 °C, 10 min, 85%; (e) TBDPSCl, imidazole, DMAP, CH_2Cl_2, room temperature, 97%; (f) 10 mol % $Pd-CaCO_3$ (Pb-poisoned), quinoline, EtOAc, room temperature, >95%; (g) toluene, 100 °C, 2 h, >95%.

to provide 3-bromo-2-phenylsulfonylpropene, which in turn reacts with phenol **21**. Upon heating the resultant phenyl ether **23** to 165 °C, a facile Claisen rearrangement occurred. Remarkably, only the desired regioisomer **24** was obtained in 94% yield.

We next studied means to cleave the phenylsulfonyl group of **24** in a reductive fashion. Several preliminary attempts in this regard were not successful. Presumably these failures reflected side reactions open to the radicaloid or carbanionic species formed upon desulfonylation of **24**. Thus, we developed the two-step procedure for removal of the phenyl sulfone. Compound **24** was first converted to **25** via conjugate addition of the phenolic oxygen to the α,β-unsaturated sulfone. Reductive elimination of the sulfonyl group, by the action of sodium amalgam, resulted in the desired **17** in 87% yield.[20] Thus, the reaction sequence had provided **17** from **21**, without contamination from the para Claisen rearrangement product, in 69% yield over four steps.

With the ortho Claisen rearrangement accomplished, focus shifted to the introduction of the reverse prenyl group onto the C_3 phenol and to the conversion of the methoxycarbonyl linkage to a C_1 hydroxyl group (Scheme 5). In the event, excess MeLi reacted with the ester function to give tertiary alcohol **26** in 90% yield. The phenolic hydroxyl group in this compound was alkylated under standard conditions (K_2CO_3, KI, 3-chloro-3-methylbut-1-yne).[21] Unfortunately, the yields of this heterogeneous O-alkylation were variable, especially for large-scale operations. After considerable experimentation, a copper-catalyzed reaction proved to be more reliable on scale-up.[22] Thus, by adding a homogeneous solution of DBU and propargyl trifluoroacetate with a catalytic amount of $CuCl_2{\cdot}H_2O$ at room temperature to **26**, the desired product **27** was isolated in 68% yield on multigram scale.

Alkylation of the C_3 phenol had now provided the proper setting to liberate the C_1-based phenolic hydroxyl group from its precursor tertiary alcohol. Accordingly, **27** was exposed to the action of concentrated H_2O_2 in acidic conditions for a short period of time.[15] Under these conditions, the hydroperoxide **28** was apparently generated. Rearrangement of this compound afforded the desired **29** in 85% yield. Protection of its free phenolic hydroxyl as a silyl ether gave **30** in 97% yield.

In anticipation of a second ortho Claisen rearrangement step, the triple bond in **30** was reduced to olefin **31** with Lindlar's catalyst using quinoline as an additive.[12,23] Happily, warming of **31** to 100 °C, led to its rearrangement to the desired cyclohexadienone **32** in almost quantitative yield. Noteworthy was the finding that the reaction occurred, albeit slowly, even at room temperature.

With **32** in hand, attention was directed to construction of the tricyclic ring system (Scheme 6). To test the feasibility of the light-induced reaction of illicinone-A reported by Furukawa,[10] we first prepared **4** from **32** using standard synthetic manipulations. Treatment of **32** with L-Selectride, followed by acetylation and β-elimination provided illicinone-A in 82% yield for two steps. Photolysis of **4**, did indeed produce tricycloillicinone as described. However, in our hands this reaction proceeded in only 10%−15% yields.

Thus, we decided to focus on the Mn(III)-based oxidative radical reaction to generate a radical at C_2. Cyclization of **32** was conducted through the action of $Mn(OAc)_3$ and $Cu(OAc)_2$ at room temperature.[11] **32** was smoothly converted to 3-oxytricycloillicinone (**9**) in 80% yield. Presumably, during this reaction, the silyl enol ether was cleaved. The resultant β-diketone then underwent oxidative cyclization as shown in Scheme 2.

With the entire framework in place, all that remained to complete the total synthesis of **1** was 4-electron reduction of the ketone at C_3 to the corresponding methylene group. In practice, this goal turned out to be an extremely difficult task. We first attempted deoxygenation directly from ketone **9** through thioketal[24] or hydrazone[25] derivatives. Unfortunately, these classical methods failed at the level of the syntheses of the required intermediates. Accordingly, we evaluated the probability of the Barton−McCombie deoxygenation protocol for

(20) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Kocienski, P.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Kocienski, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, New York, Seoul, Tokyo; 1991; Vol. 6, p 975.

(21) Hlubucek, J.; Ritche, E.; Tayler, W. C. *Tetrahedron Lett.* **1969**, 1369.

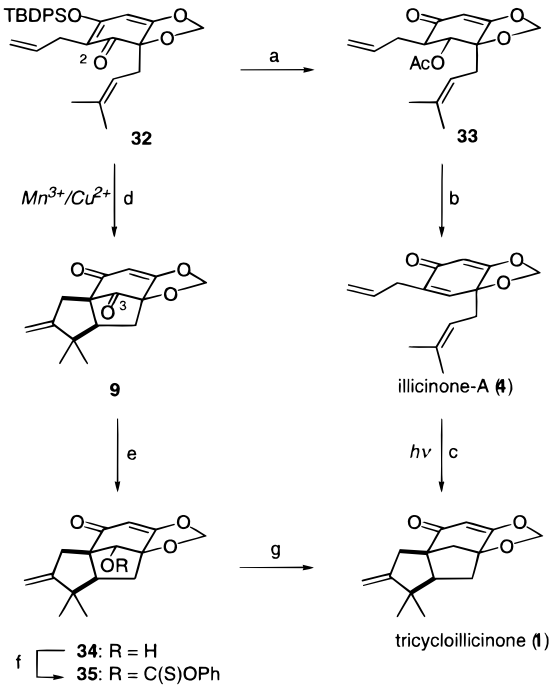
(22) (a) Godfrey, J. D., Jr.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405. (b) Bell, D.; Davies, M. R.; Geen, G. R.; Mann, I. S. *Synthesis* **1995**, 707.

(23) (a) Lindlar, H. *Helv. Chim. Acta*. **1952**, *35*, 446. (b) McEwen, A. B.; Guttieri, M. J.; Maier, W. F.; Laine, R. M.; Shyo, Y. *J. Org. Chem.* **1983**, *48*, 4436.

(24) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc*. **1980**, *102*, 7612.

(25) (a) Wolff, L. *Justus Liebigs Ann. Chem*. **1912**, *394*, 86. (b) Huang, M. L. *J. Am. Chem. Soc*. **1946**, *68*, 2487.

Scheme 6.[a] Completion of the Total Synthesis of Tricycloillicinone



[a] Reagents and conditions: (a) (i) L-Selectride, THF, 0 °C, 3 h; then *p*-TsOH, 0 °C, 2 h; (ii) Ac_2O, DMAP, 0 °C, 3 h, 82% overall; (b) neat DBU, room temperature, 1 h, 65%; (c) degassed Et_2O, 450-W Hg lamp, Pyrex tube, 1 h, 10−15% (see ref 10); (d) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc, room temperature, overnight, 80%; (e) LiAlH(O-*t*-Bu)$_3$, THF, 78%; (f) KHMDS, THF, −78 °C, then DMAP, PhOC(S)Cl, −20 °C, overnight, 90%; (g) Bu_3SnH, AIBN, benzene, 80 °C, overnight, 42%.

our needs.[26] Selective reduction of the isolated ketone, over the α,β-unsaturated ketone, was achieved via the action of LiAlH(O*t*-Bu)$_3$ (Scheme 6). However, the secondary alcohol in **34** proved to be extremely resistant to activation. For instance, under standard conditions (excess PhOC(S)Cl and DMAP), the thioformate **35** failed to form. After extensive experimentation, we were able to reach **35** under more forcing conditions. Compound **34** was first converted to its potassium salt using KHMDS. The latter, in turn reacted with PhOC(S)Cl and DMAP, providing the desired **35** in 90% yield.

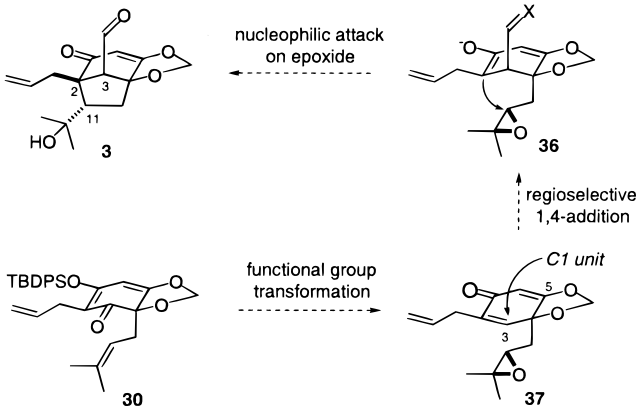
Radical deoxygenation of **35** was carefully conducted on a small scale using excess Bu_3SnH to provide **1** in 42% yield. The synthetic tricycloillicinone (racemate) was identical to the authentic natural product by the criteria of ^1H, ^{13}C NMR and IR spectroscopy. In addition to producing the natural product in a more pleasing fashion, this oxidative radical route provides access to a wealth of analogue structures.

Synthetic Plan for Bicycloillicinone Aldehyde (3)

Having successfully developed a flexible strategy for the synthesis of tricycloillicinone, we were in a position to pursue the construction of other neurotrophic illicinones. In this connection, bicycloillicinone asaronacetal (**2**) attracted our attention. Its structure is different from that of **1** in that it contains an additional carbon branch at C_3. The formyl group at this position is actually encumbered in the form of an unusual catechol acetal (see structure **2** in Figure 1). To pursue the total synthesis of **2**, we decided to develop a potentially novel solution

(26) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

Scheme 7. Synthetic Strategy of Bicycloillicinone Aldehyde (**3**)



for constructing aldehyde **3**, which is also an acid-induced degradation product of the natural product **2**. It is well to note that tricycloillicinone has a cis relationship between C_2 and C_{11}; **3** has a trans relationship. A new departure for the ring construction was thus appropriate.

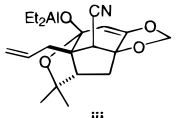
Our retrosynthetic logic to reach **3** is suggested in Scheme 7. We planned to construct the five-membered ring by nucleophilic cyclization of kinetically generated C_2 enolate via the epoxide linkage in **36**. Thus, ring closure would concurrently expose the tertiary alcohol. Compound **36** might arise from a regioselective 1,4-addition of a one-carbon unit to C_3 over C_5 in an axial manner, either with or without trapping of the resultant enolate. In consideration of the potential hindrance at C_3, we chose to rely on the Nagata reagent (Et_2AlCN) for this purpose.[27] This nucleophile would hopefully be relatively nonvulnerable to steric blockade. It was anticipated that **37** could be prepared from a synthetic intermediate on the route to tricycloillicinone.

Synthesis of Bicycloillicinone Aldehyde 3

The synthesis began with **33** (Scheme 8). Selective epoxidation of the prenyl moiety was achieved using mCPBA at 0 °C. The reaction gave an inseparable 2:1 mixture of epoxides **38**, favoring the desired isomer in 72% yield. DBU-induced β-elimination of the acetoxy group provided precursor **39** in 60% yield. The crucial 1,4-addition of cyanide to **39** was conducted using 2 equiv of Et_2AlCN in THF at 0 °C. Not only did the cyano nucleophile add to the C_3 position of **39** selectively but the resultant kinetically generated metaloenolate attacked the epoxide, thereby furnishing cyclized products **41** (87% from the β-epoxide) and **42** (81% from the α-epoxide). Fortunately, **41** and **42** were separable by silica gel column chromatography, and the structures of these compounds were unambiguously determined by NMR spectroscopy. Interestingly, only the undesired isomer underwent a second 1,4-addition, leading to bis(nitrile) **42**.[28] To our knowledge, reaching **41** in this way constitutes the first example of using a Nagata reaction in such

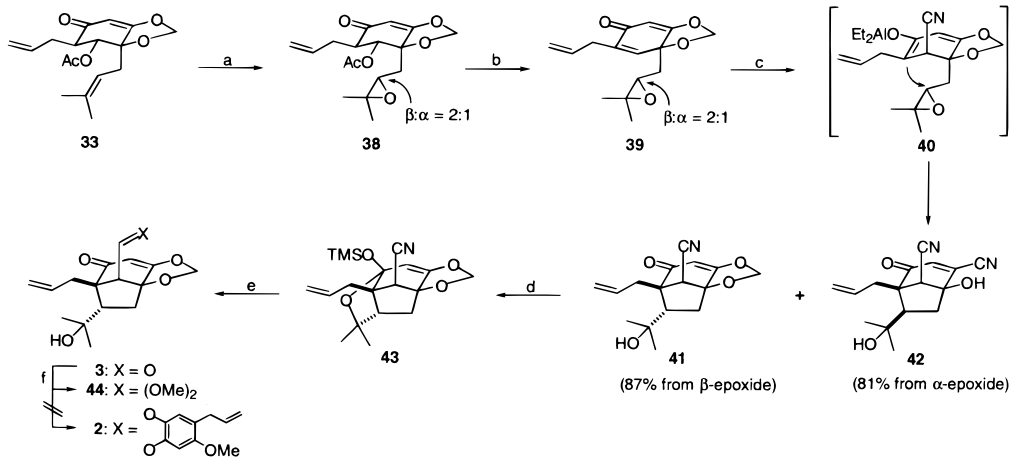
(27) (a) Nagata W.; Yoshikawa, M. *Organic Reaction*; Dauben, W. G., Ed.; Wiley and Sons: New York, 1984; Vol. 25, p 225. For a recent application of Nagata reaction, see: (b) Ihara, M.; Katsumata, A.; Egashira, M.; Suzuki, S.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 5560.

(28) Selective monocyanide addition to **41** could be explained as the formation of aluminum acetal **iii** after the reaction.



iii

Scheme 8..[a] Synthesis of Bicycloillicinone Aldehyde (**3**)



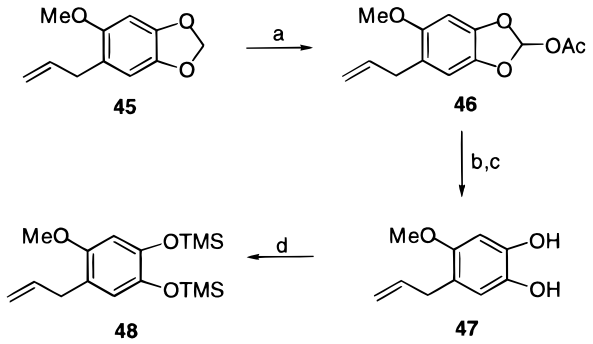
[a] Reagents and Conditions: (a) mCPBA, CH_2Cl_2−5% aqueous $NaHCO_3$, 0 °C to room temperature, 3 h, 73%; (b) DBU, THF, 0 °C to room temperature, 2.5 h, 60%; (c) Et_2AlCN, THF, 0 °C, 40 min, 58% (**41**), 27% (**42**); (d) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (e) DIBAL, hexane-CH_2Cl_2 (2:1), −90 °C, 30 min; AcOH, CH_3OH, room temperature, 2 h, 69% from **41**; (f) TMSOMe, TMSOTf, CH_2Cl_2, −78 °C to 0 °C, 40 min, 49%.

a tandem sequence.[29] While an epoxide opening by an aluminum keto−enolate had been reported by Schreiber,[30] such metal-mediated additions are certainly less developed[31] relative to their ester enolate counterparts.[32]

With **41** in hand, the only remaining step to reach **3** was that of controlled reduction of the nitrile function to produce the aldehyde. However, in practice, achievement of this transformation turned out to be no trivial matter. Standard reducing agents resulted in 1,2- or 1,4-reduction of the α,*β*-unsaturated ketone but failed to reduce the nitrile. Given these results, a method for protecting the ketone in **41** was pursued. Recognition that the tertiary alcohol in **41** is located "underneath" the ketone function suggested the possibility of protection of the ketone by formation of an internal ketal. Gratifyingly, treatment of **41** with TMSOTf in the presence of base selectively led to the TMS acetal **43**. Without purification, this intermediate was submitted to DIBAL reduction in hexane−CH_2Cl_2. Indeed following acidic workup, the desired aldehyde **3** was obtained in 69% overall yield. It is worth noting that the hexane content is crucial for success of the DIBAL reduction. Thus, the starting material was completely recovered using other solvent systems (THF, toluene, CH_2Cl_2). The fully synthetic aldehyde **3** was identical to the hydrolysis product of **2** by ^1H, ^{13}C NMR and IR spectroscopic criteria.

For a preliminary study directed to the possibility of the catechol acetalization of **3** required to synthesize **2**, the catechol **47** and bis-TMS catechol **48** were prepared from the known compound **45**[33] (see Scheme 9). However, under a variety of conditions, attempted coupling of aldehyde **3** and derivatives **47** or **48** resulted in significant decomposition. A common byproduct (vide infra) was isolated from each reaction. We found that methyl acetal **44** could be prepared in 49% yield by using Noyori conditions (Scheme 8).[34] Even in this reaction, the same byproduct was obtained as a minor component. Eventually, its structure was elucidated to be **49** (Scheme 10).

Scheme 9.[a] Synthesis of the Catechol Moiety



[a] Reagents and Conditions: (a) $Pb(OAc)_4$, PhH, 60 °C, 4 h (see ref 36); (b) AcOH−H_2O−THF, 0 °C to room temperature, 1.5 h; (c) MeOH, room temperature, 1 h, 75% (three steps); (d) $HN[Si(CH_3)_3]_2$, cat. H_2SO_4, THF, reflux, 30 min.

A plausible mechanistic rationalization of the formation of this compound is shown. These preliminary investigations have revealed that aldehyde **3** is relatively unstable to strongly acidic media. Completion of total synthesis of **2** would require avoidance of acidic conditions. Several schemes intended to reach this goal have failed and the total synthesis of **2**, bearing the catechol acetal, still awaits realization.[35]

Summary

A concise total synthesis of tricycloillicinone has been achieved from commercially available methyl 3,4,5-trihydroxybenzoate in 15 steps. This synthesis employed new strategies to control the regiochemistry of two key Claisen rearrangements. A cumyl hydroperoxide rearrangement reaction simplified the protecting group management issue. Application of the Corey−Snider oxidative cyclization and the Barton−McCombie deoxy-

(29) Further work to study the generality of this aluminum enolate epoxide opening reaction is in progress.

(30) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165.

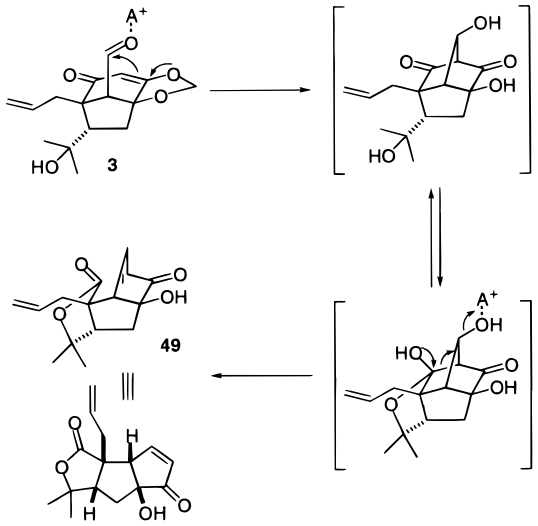
(31) Metal-mediated reaction of ketone enolate to epoxide has been extensively studied by Crotti and associates: (a) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583. (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M. *J. Org. Chem.* **1996**, *61*, 9548. (c) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 6537. (d) Crotti, P, Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano E. *Tetrahedron* **1999**, *55*, 5853.

(32) For representative examples of aluminum ester enolate addition to epoxide, see: (a) Danishefsky, S.; Kitahara, T.; Tsai, M.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1669. (b) Taylor, S. K.; Fried, J. A.; Grassl, Y. N.; Marolewski, A. E.; Pelton, E. A.; Poel, T.-J.; Rezanka, D. S.; Whittaker, M. R. *J. Org. Chem.* **1993**, *58*, 7304.

(33) Compound **45** was synthesized in three steps from commercially available sesamol: (a) Alexander, B. H.; Gertler, S. I.; Brown, R. T.; Oda, T. A.; Beroza, M. *J. Org. Chem.* **1959**, *4*, 49. (b) Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972.

(34) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

Scheme 10. Possible Decomposition Pathway of **3** in Acidic Media



genation sequence provided a direct route to tricycloillicinone. For bicycloillicinone aldehyde **3**, we employed a new tandem reaction using the Nagata reagent to construct the cage structure and the tertiary alcohol simultaneously. These flexible syntheses of the polycyclic illicinones should provide access to analogous structures for future biological and SAR studies.

Experimental Section

General Methods. All commercial materials (purchased from Aldrich-Sigma) were used without further purification. The following solvents were obtained from a dry solvent system (passed through a column of alumina): THF, diethyl ether (Et_2O), CH_2Cl_2, toluene, and benzene. All reactions were performed under an atmosphere of argon. Powdered molecular sieves (4 Å) were charged by flame drying under high vacuum for 20 min. NMR (^1H and ^{13}C) spectra were recorded on a Bruker AMX-400 MHz or Bruker DRX-500 MHz and referenced to residual solvent unless otherwise noted. IR spectra were recorded with a Perkin-Elmer 1600 series FTIR spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 HF mass spectrometer, and low-resolution mass spectra were recorded on a Nermag R10-10 mass spectrometer. Analytical TLC was performed on E. Merck silica gel 60 F254 plates, and flash column chromatography was performed using indicated solvents on E. Merck silica gel 60 (40−63 μm).

Allyl Ether 23. Phenol **21** (5 g, 25 mmol) was dissolved in acetone (250 mL), and solid potassium carbonate (10.3 g, 75 mmol) was added. The suspension was stirred for 10 min at room temperature and then treated with 1,3-dibromo-2-phenylsulfonylpropane (9.6 g, 28 mmol) and potassium iodide (100 mg, 0.60 mmol). The mixture was stirred at room temperature for 12 h. The suspension was filtered through Celite and concentrated. Flash column chromatography (hexane−ether 90:10) gave allyl ether **23** (8.4 g, 87%): IR (neat) 2953, 1697, 1612, 1420, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (2H, m), 7.65 (1H, m), 7.55 (2H, m), 7.18 (1H, d, J = 1.3 Hz), 7.08 (1H, d, J = 1.3 Hz), 6.59 (1H, s), 6.22 (1H, s), 5.96 (2H, s), 4.84 (2H, t, J = 1.3 Hz), 3.44 (3H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.4, 149.5, 146.4, 141.1, 139.9, 139.5, 134.2, 129.7, 128.6, 127.1, 125.0, 113.0, 105.0, 102.6, 66.5, 52.6; HRMS calcd for $C_{18}H_{16}O_7S$ [M]$^+$ 376.0617, found 376.0629; LRMS 376, 219, 203, 165, 141, 125.

Phenol 24. Allyl ether **23** (8.4 g, 22 mmol) in a pressure tube was heated at 165 °C for 12 h. After being cooled to room temperature, the crude product was used in the following reaction without further purification: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.89 (2H, d, J = 7.5 Hz), 7.62 (1H, t, J = 7.5 Hz), 7.54 (2H, t, J = 7.5 Hz), 7.03 (1H, s), 6.34 (1H, s), 6.01 (1H, s), 5.92 (1H, s), 5.55 (1H, s), 3.95 (2H, s), 3.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.8, 150.4, 147.6, 139.9, 139.2, 138.4, 133.7, 129.4, 128.6, 124.6, 122.7, 122.0, 103.4, 102.5, 51.8, 27.1; HRMS calcd for $C_{18}H_{16}O_7S$ [M]$^+$ 376.0617, found 376.0616.

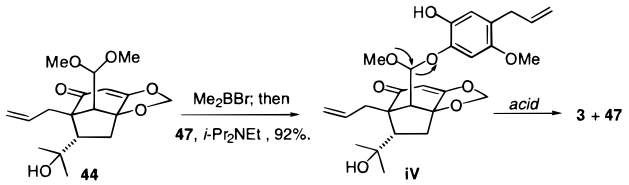
Sulfone Ether 25. The above phenol **24** was converted into sulfone ether **25** by refluxing in acetone with K_2CO_3. After an aqueous workup, the residue was subjected to flash column chromatography (hexane−ether 90:10) to give sulfone ether **25** (7.9 g, 94% for two steps): IR (neat) 2920, 2880, 1695, 1618, 1490, 1470, 1430, 1421, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (2H, m), 7.64 (1H, m), 7.55 (2H, m), 7.13 (1H, s), 5.98 (2H, s), 4.58 (1H, dd, J = 11.0, 3.3 Hz), 4.24 (1H, dd, J = 11.0, 8.5 Hz), 3.81 (3H, s), 3.57 (1H, m), 3.47 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.3, 146.6, 138.4, 138.1, 137.1, 134.2, 129.3, 129.0, 122.4, 118.2, 105.3, 102.5, 63.5, 57.9, 52.0, 24.6; HRMS calcd for $C_{18}H_{16}O_7S$ [M]$^+$ 376.0617, found 376.0618; LRMS 376, 234, 219, 203, 175, 145, 133, 104, 77.

Phenol 17. Sulfone ether **25** (7.9 g, 21 mmol) was dissolved in EtOAc−MeOH (2:1) and cooled to −20 °C. Solid sodium amalgam (10%, 40 g, 52 mmol) was added to this solution, and the resultant mixture was stirred for 12 h at −20 °C. The reaction mixture was quenched by solid citric acid, diluted with ether, and washed with saturated aqueous $NaHCO_3$. Drying over Na_2SO_4, concentration, and flash column chromatography (hexane−ether 80:20) gave phenol **17** (4.2 g, 86%): IR (neat) 3300, 1675, 1425, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.06 (1H, s), 6.00 (2H, s), 5.99 (1H, m) 5.06 (1H, dd, J = 7.2, 1.5 Hz), 5.03 (1H, s), 4.98 (1H, s), 3.83 (3H, s), 3.77 (2H, dt, J = 6.0, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 167.8, 146.8, 138.6, 138.1, 137.1, 125.5, 124.0, 115.7, 104.4, 102.6, 52.4, 31.0; HRMS calcd for $C_{12}H_{12}O_5$ [M]$^+$ 236.0685, found 236.0686; LRMS 254, 237.

Tertiary Alcohol 26. Ester **17** (4.2 g, 18 mmol) was dissolved in THF and cooled to −78 °C. MeLi (72 mL, 1 M in THF with LiBr) was added dropwise to this solution at −78 °C. The solution was allowed to warm to 0 °C and stirring was continued for 12 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the organic layer was dried over Na_2SO_4. Concentration and flash column chromatography (hexane−ether 90:10) gave tertiary alcohol **26** (3.8 g, 90%): IR (neat) 3421, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.64 (1H, s), 6.07 (1H, m), 5.93 (2H, s), 5.11 (1H, dd, J = 10.1, 1.6 Hz), 5.02 (1H, dd, J = 17.0, 1.6 Hz), 4.96 (1H, s), 3.81 (2H, dt, J = 5.2, 1.6 Hz), 1.73 (1H, s), 1.60 (3H, s), 1.59 (3H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 140.3, 139.1, 137.9, 119.2, 115.4, 102.7, 101.5, 73.8, 31.9, 31.5 (2 unresolved); HRMS calcd for $C_{13}H_{16}O_4$ [M]$^+$ 236.1048, found 236.1042; LRMS 236, 221, 218, 203, 173, 145, 115.

Propargyl Ether 27. To a solution of 2-methyl-3-butyn-2-ol (970 μM, 10 mmol) in CH_3CN (10 mL) at 0 °C was added DBU (1.7 mL, 11.3 mmol), followed by dropwise addition of $(CF_3CO)_2O$ (1.4 mL, 10 mmol). To the above solution was added phenol **26** (1.5413 g, 6.5 mmol), DBU (2.4 mL, 16.0 mmol), and $CuCl_2 \cdot H_2O$ (6.7 mg, 0.039 mmol) in CH_3CN (30 mL). After being stirred at room temperature for 24 h, the solution was evaporated, diluted with EtOAc, and washed with H_2O, saturated aqueous $NaHCO_3$, and brine. Flash column chromatography (hexanes−EtOAc 90:10−70:30) gave propargyl ether **27** (1.344 g, 68%) along with recovered starting material **26** (0.178 g, 11%): IR (neat) 3480, 3281, 2957, 2116 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.76 (1H, s), 6.04 (1H, m), 5.87 (2H, s), 4.96 (1H, dd, J = 10.2, 1.8 Hz), 4.82 (1H, dd, J = 17.0, 1.8 Hz), 3.82 (2H, dt, J = 5.2, 1.8 Hz), 2.37 (1H, s), 1.95 (1H, s), 1.72 (6H, s), 1.58 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.5, 140.0, 139.7, 138.54, 138.45, 127.6, 114.3, 102.5, 100.7, 85.2, 75.8, 73.9, 73.6, 32.3, 32.0, 30.4; HRMS

(35) Methyl acetal **44** was successfully converted to mixed acetal **50** via bromination, followed by treatment with catechol **47** in the presence of base. Unfortunately, all attempts to close the five-membered ring of **iv** to **2** was unsuccessful. For instance, acid-induced reactions of **iv** typically gave aldehyde **3** and catechol **47**.



(36) Ikeya, Y.; Taguchi, H.; Yoshioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 2893.

calcd for $C_{18}H_{22}O_4$ $[M]^+$ 302.1518, found 302.1515; LRMS 302, 221, 218, 203.

Phenol 29. Tertiary alcohol **27** (3.5 g, 11.8 mmol) was dissolved in CH_2Cl_2 (400 mL) and cooled to 0 °C. To this solution was added dropwise a precooled (0 °C) mixture of concentrated sulfuric acid (45 mL) and 50% H_2O_2 (50 mL). After 10 min at 0 °C, the reaction mixture was diluted with water, and the organic layer was washed successively with saturated aqueous $Na_2S_2O_4$ and saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Flash column chromatography (hexane−ether 90:10) gave the desired phenol **29** (2.6 g, 85%): IR (neat) 3499, 3288, 2985, 2250, 1633, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.28 (1H, s), 5.94 (1H, m), 5.84 (2H, s), 5.18 (1H, dd, J = 17.2, 1.6 Hz), 5.15 (1H, dd, J = 10.1, 1.6 Hz), 4.94 (1H, s), 3.46 (2H, dt, J = 6.0, 1.6 Hz), 2.41 (1H, s), 1.69 (6H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.6, 147.0, 136.8, 136.7, 134.7, 116.2, 113.5, 100.5, 95.3, 85.3, 76.2, 73.7, 30.1, 29.3; HRMS calcd for $C_{15}H_{16}O_4$ $[M]^+$ 260.1049, found 260.1037.

TBDPS Ether 30. Phenol **29** (2.6 g, 10 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with TBDPSCl (2.8 mL, 10.8 mmol), imidazole (735 mg, 10.8 mmol), and dimethylaminopyridine (25 mg). After 12 h at room temperature, the solvent was removed and the residue was directly subjected to flash column chromatography (hexane−ether 95:5) to give the desired silyl ether **30** (4.9 g, 97%): IR (neat) 2931, 2180, 1469 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (4H, m), 7.39 (2H, m), 7.34 (4H, m), 6.02 (1H, m), 5.86 (1H, s), 5.69 (2H, s), 5.02 (1H, dd, J = 17.1, 1.8 Hz), 4.98 (1H, dd, J = 10.2, 1.8 Hz), 3.55 (2H, dt, J = 5.8, 1.5 Hz), 2.39 (1H, s), 1.70 (6H, s), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 147.9, 145.9, 143.6, 137.3, 137.1, 135.4, 134.4, 132.7, 129.8, 127.7, 118.7, 114.3, 100.3, 97.7, 85.5, 75.7, 73.3, 30.2, 29.4, 26.5, 19.4; HRMS calcd for $C_{31}H_{34}O_4Si$ $[M]^+$ 498.2226, found 498.2219.

Allyl Ether 31. Propargyl ether **30** (1 g, 2 mmol) was dissolved in ethyl acetate (10 mL), and Lindlar's catalyst (10% Pb-poisoned, 50 mg) and quinoline (50 μL) were added. The suspension was stirred under hydrogen for 2 h, filtered through Celite, concentrated, and subjected to flash column chromatography (hexane−ether 95:5) to give the allyl ether **31** (990 mg, 99%): IR (neat) 2931, 1621 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.67 (4H, dd, J = 7.5, 1.1 Hz), 7.40 (2H, t, J = 7.5 Hz), 7.34 (4H, t, J = 7.5 Hz), 6.11 (1H, dd, J = 17.4, 10.8 Hz), 6.01 (1H, m), 5.83 (1H, s), 5.66 (2H, s), 5.18 (1H, d, J = 17.4 Hz), 5.01 (3H, m), 3.47 (2H, d, J = 5.8 Hz), 1.46 (6H, s), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 148.1, 145.9, 143.6, 137.6, 137.2, 135.5, 132.7, 129.8, 127.7, 127.5, 118.3, 114.3, 112.7, 100.1, 97.1, 81.9, 31.5, 27.0, 26.5, 19.4; HRMS calcd for $C_{31}H_{36}O_4Si$ $[M]^+$ 500.2383, found 500.2390.

Cyclohexadienone 32. Allyl ether **31** (250 mg, 0.5 mmol) was dissolved in toluene (10 mL) and heated at 100 °C for 2 h. Concentration gave the rearranged product **32** (250 mg, 100%), which was used in the following reaction without further purification: IR (neat) 3073, 2960, 2931, 2859, 1684, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (4H, m), 7.44 (6H, m), 5.88 (1H, m), 5.41 (1H, s), 5.35 (1H, s), 5.11−4.95 (3H, m), 4.78 (1H, s), 3.26 (1H, dd, J = 14.8, 6.2 Hz), 3.13 (1H, ddt, J = 14.8, 6.2, 1.4 Hz), 2.58 (1H, dd, J = 14.5, 7.5 Hz), 2.48 (1H, dd, J = 14.5, 7.1 Hz), 1.67 (3H, s), 1.55 (3H, s), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1, 167.3, 165.2, 137.3, 136.5, 135.5, 132.3, 130.9, 128.7, 128.6, 128.5, 116.3, 114.9, 111.5, 99.3, 91.8, 87.9, 35.6, 27.3, 26.9, 26.3, 19.8, 18.3; HRMS calcd for $C_{31}H_{37}O_4Si$ $[M + H]^+$ 501.2461, found 501.2452.

Acetate 33. Cyclohexadienone **32** (250 mg, 0.5 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Lithium tri-*sec*-butylborohydride (1.0 M in THF, 0.5 mL, 0.5 mmol) was added to this mixture, and the resultant solution was stirred for 3 h at 0 °C. The reaction mixture was quenched by *p*-toluenesulfonic acid (250 mg) and stirred for 2 h at 0 °C. Concentration gave the crude alcohol, which was used in the following reaction without further purification: IR (neat) 3406, 1651, 1643, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.73 (1H, m), 5.55 (1H, s), 5.53 (1H, s), 5.51 (1H, s), 5.25 (1H, m), 5.18−5.05 (2H, m), 4.14 (1H, dd, J = 11.2, 3.7 Hz), 2.83 (2H, m), 2.61 (2H, m), 2.45 (1H, m), 2.32 (1H, d, J = 3.7 Hz), 1.75 (3H, s), 1.67 (3H, s).

The above alcohol was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. Acetic anhydride (0.25 mL) and DMAP (250 mg) were added to this mixture, and the resultant solution was stirred for 3h at 0 °C. Concentration and flash column chromatography (hexane−ether 95:5) gave acetate **33** (125 mg, 82%): IR (neat) 1735, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 5.64−5.58 (2H, m), 5.59 (1H, s), 5.55 (1H, s), 5.53 (1H, s), 5.18 (1H, m), 5.06 (1H, s), 5.01 (1H, d, J = 5.1 Hz), 2.78−2.51 (4H, m), 2.35 (1H, m), 2.17 (3H, s), 1.73 (3H, s), 1.69 (3H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 196.0, 173.4, 170.0, 137.3, 134.2, 118.7, 116.8, 101.2, 99.8, 85.8, 74.5, 48.4, 32.4, 30.7, 26.4, 21.3, 18.4; HRMS calcd for $C_{17}H_{22}O_5$ $[M]^+$ 306.1467, found 306.1454.

Illicinone-A (4). To acetate **33** (62 mg, 0.21 mmol) at 0 °C was added DBU (0.5 mL), and the reaction was warmed to room temperature. The solution was stirred for 3 h and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane−EtOAc 85:15) gave **4** (33 mg, 65%): IR (neat) 1665, 1630, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.62 (1H, s), 5.81 (1H, m), 5.65 (1H, s), 5.62 (1H, s), 5.55 (1H, s), 5.13 (2H, m), 5.01 (1H, m), 3.07 (2H, m), 2.51 (1H, dd, J = 17.4, 9.5 Hz), 2.41 (1H, dd, J = 17.4, 10.0 Hz), 1.69 (3H, s), 1.53 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.9, 173.7, 139.4, 137.7, 134.8, 134.4, 117.3, 115.9, 98.4, 98.0, 82.1, 34.8, 33.4, 25.9, 17.9; HRMS calcd for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1267; LRMS 246, 203, 188, 178, 150, 147.

Irradiation of Illicinone-A. A solution of illicinone-A (30 mg, 0.14 mmol) in a Pyrex test tube was degassed and exposed to light emitted from a 450-W Hg lamp for 1 h. Flash column chromatography gave **1** (3 mg), the tetracyclic compound **6** (4 mg), and recovered illicinone-A (20 mg). Prolonged exposure resulted in significant decomposition of tricycloillicinone: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.64 (1H, s), 5.45 (1H, s), 5.27 (1H, s), 4.85 (1H, s), 4.78 (1H, s), 3.32 (1H, dt, J = 15.6, 2.1 Hz), 2.00−2.25 (4H, m), 1.84−1.93 (2H, m), 1.10 (3H, s), 1.07 (3H, s); HRMS calcd for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1251; LRMS 246, 231, 216, 201, 188, 173.

Oxytricycloillicinone (9). $Mn(OAc)_3 \cdot 2H_2O$ (181 mg, 0.675 mmol) and $Cu(OAc)_2 \cdot H_2O$ (66 mg, 0.330 mmol) were suspended in AcOH (3.0 mL), and cyclohexadienone **32** (154 mg, 0.307 mmol) was added to this suspension. The reaction mixture was stirred at room temperature for 12 h and diluted with EtOAc. The organic layer was washed with H_2O, saturated $NaHCO_3$, H_2O, and brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane−ether 85:15) gave **9** (66 mg, 76%): IR (neat) 3100, 3063, 2970, 1772, 1670, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (1H, s), 5.64 (1H, s), 5.62 (1H, s), 4.90 (1H, s), 4.78 (1H, s), 3.13 (1H, d, J = 16.8 Hz), 2.87 (1H, dt, J = 16.8, 2.2 Hz), 2.35 (1H, dd, J = 12.5, 10.2 Hz), 2.18 (1H, dd, J = 10.2, 6.1 Hz), 2.06 (1H, dd, J = 12.5, 6.1 Hz), 1.07 (3H, s), 0.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 193.2, 174.8, 158.0, 105.7, 101.4, 98.7, 90.8, 67.5, 51.6, 45.4, 27.9, 27.1, 26.5, 24.0; HRMS (FAB) calcd for $C_{15}H_{16}O_4$ $[M]^+$ 260.1049, found 260.1038.

Alcohol 34. **9** (42 mg, 0.161 mmol) was dissolved in THF (5 mL), and $LiAlH(O\text{-}t\text{-}Bu)_3$ (1.0 M solution in THF, 185 μL, 0.185 mmol) was added at −78 °C. The reaction mixture was stirred at −78 to 0 °C for 3 h and then was quenched with acetone. The organic layer was diluted with Et_2O, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and flash column chromatography (hexane−ether 70:30) gave alcohol **34** (40 mg, >95% yield): IR (neat) 3420, 3058, 2958, 1668, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (1H, s), 5.47 (1H, s), 5.37 (1H, s), 4.87 (1H, s), 4.74 (1H, s), 3.82 (1H, d, J = 3.5 Hz), 3.30 (1H, dt, J = 15.4, 2.2 Hz), 2.49 (1H, d, J = 16.4 Hz), 2.43 (1H, d, J = 3.5 Hz), 2.30 (1H, m), 2.06 (2H, m), 1.17 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 176.0, 162.6, 103.8, 100.0, 97.1, 92.2, 79.8, 63.3, 54.9, 43.5, 32.3, 30.7, 28.1, 24.5; HRMS (FAB) calcd for $C_{15}H_{18}O_4$ $[M]^+$ 262.1205, found 262.1212.

Xanthate 35. To a solution of alcohol **34** (14.0 mg, 0.053 mmol) in THF (2 mL) was added KHMDS (0.5 M in toluene, 0.75 mL, 0.375 mmol) at −78 °C. The solution stirred at −78 °C for 30 min. This solution was added to the salt of DMAP (52 mg, 0.42 mmol) and PhOC(S)Cl (59 μL, 0.42 mmol) in THF (4 mL) at −20 °C, and the resultant mixture was stirred overnight at the same temperature. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Concentration and flash column chromatography (hexane−ether 80:20) gave desired **35** (21 mg, >95% yield): IR (neat) 2962, 1674, 1640, 1480 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40

(2H, t, $J = 7.6$ Hz), 7.28 (1H, t, $J = 7.6$ Hz), 7.08 (2H, d, $J = 7.6$ Hz), 5.70 (1H, s), 5.66 (1H, s), 5.53 (1H, s), 5.49 (1H, s), 4.84 (1H, s), 4.72 (1H, s), 3.35 (1H, dt, $J = 16.8$, 2.5 Hz), 2.53 (1H, d, $J = 16.8$ Hz), 2.37 (1H, dd, $J = 12.1$, 7.3 Hz), 2.22 (1H, dd, $J = 11.2$, 2.7 Hz), 2.15 (1H, dd, $J = 16.5$, 9.2 Hz), 1.17 (3H, s), 1.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 160.8, 129.5, 126.7, 121.7, 102.6, 99.9, 97.4, 89.7, 87.1, 63.3, 54.6, 43.0, 33.1, 31.4, 29.5, 23.9; HRMS (FAB) calcd for $C_{22}H_{23}O_5S$ $[M + H]^+$ 399.1267, found 399.1281.

Tricycloillicinone (1). To a solution of xanthate **35** (7.0 mg, 0.0176 mmol) in benzene (2 mL) were added Bu_3SnH (35 mg, 0.12 mmol) and AIBN (1.4 mg, 0.0085 mmol). The solution was degassed twice and heated at 60 °C for 7 h. Concentration and flash column chromatography (hexane−ether 85:15) gave **1** (1.8 mg, 42% yield): IR (neat) 3060, 2962, 2924, 1670, 1646 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (1H, s), 5.45 (1H, s), 5.27 (1H, s), 4.85 (1H, s), 4.78 (1H, s), 3.32 (1H, dt, $J = 15.6$, 2.1 Hz), 2.00−2.25 (4H, m), 1.84−1.93 (2H, m), 1.10 (3H, s), 1.07 (3H, s); ^{1}H NMR (500 MHz, C_6D_6, $\delta_{ref} = 7.16$) δ 5.43 (1H, s), 4.90 (1H, d, $J = 0.8$ Hz), 4.77 (1H, s), 4.70 (1H, s), 4.69 (1H, s), 3.63 (1H, dt, $J = 15.5$, 2.1 Hz), 1.90 (1H, d, $J = 15.5$ Hz), 1.83 (1H, d, $J = 10.3$ Hz), 1.78 (1H, t, $J = 8.2$ Hz), 1.64 (1H, dd, $J = 10.3$, 0.8 Hz), 1.45 (2H, m), 0.93 (3H, s), 0.80 (3H, s); ^{13}C NMR (75 MHz, C_6D_6, $\delta_{ref} = 128.0$) δ 198.3, 177.0, 159.9, 105.1, 98.8, 95.3, 87.6, 56.9, 53.8, 44.8, 42.8, 35.4, 31.7, 31.4, 24.4; HRMS (FAB) calcd for $[C_{15}H_{18}O_3]^+$ 246.1256, found 246.1251; LRMS (CI) 246, 231, 216, 201, 188, 173.

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Supporting Information Available: ^{1}H and ^{13}C spectra for **1**, **3**, **4**, **9**, **23**−**27**, **29**−**35**, **38**, **39**, **41**−**43**, **47**, and **49** and ^{1}H NMR for **44** and **48**; experimental protocols leading to **3**, **36**, **39**, **41**−**44**, and **47**−**49** are available (PDF) (print/PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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