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# Toward a total synthesis of the novel neurotrophic sesquiterpene merrilactone A: a RCM and [2+2]-photocycloaddition based approach to framework construction

Goverdhan Mehta* and S. Robindro Singh

*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

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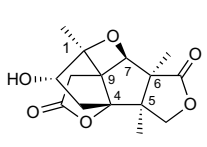
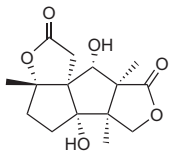
**Abstract**—A new strategy toward the total synthesis of the novel structural complex and biologically potent neurotrophic factor merrilactone A from 2,3-dimethyl-2-cyclopentene-1,4-dione is outlined. The approach involving RCM and [2+2]-photocycloaddition as the key steps, is notable for the orchestration of a series of regio- and stereoselective operations that lead to the core structural motif present in the sesquiterpenoid natural product.


With increasing life expectancy, neurodegenerative disorders are already emerging as a major health concern worldwide. In this context, neurotrophic factors like the nerve growth factor (NGF), which promote the maintenance and growth of neurons, are attracting considerable attention. Molecular entities of both synthetic and natural origin are being evaluated for neurotrophic properties as possible leads for developing therapies for neurodegenerative disorders.[1] In 2000, the group of Fukuyama and co-workers[2] reported the isolation of a novel pentacyclic sesquiterpene merrilactone A **1** from the pericarps of *Illicium merrillianum*, a plant indigenous to China and Myanmar, in 0.004% yield and determined its structure (X-ray) and absolute configuration (Mosher). It was further shown[2] that **1** significantly promotes neurite outgrowth in the primary cultures of fetal rat cortical neurons from concentrations as low as 0.1–10 μmol. These promising biological attributes in conjunction with the compact, densely oxygenated pentacyclic architecture of **1**, with seven stereogenic centers, two γ-lactone moieties and four quaternary carbon atoms, make it an attractive and challenging synthetic target.




**1** Merrilactone A




**2** Anislactone A

Not surprisingly, merrilactone A **1** has elicited enthusiastic responses from synthetic chemists and two elegant total syntheses by Birman and Danishefsky[3] in 2002 and by Hirama and co-workers[4] in 2003 have already been accomplished, although in racemic form. We report here our own forays toward **1** that have culminated in the rapid and efficient construction of the core structure present in the natural product. The strategy outlined here toward **1** is also amenable to adaptation for the synthesis of related sesquiterpenoids like anislactone A **2**.[5]

In designing an approach to **1**, we initially focused on the two main structural motifs; the tricyclic oxa[3.3.3]propellane framework built on C4 and C9 and the installation of the C5, C6 quaternary carbon centers (the natural product numbering scheme as shown in **1** has been followed throughout).[2] In this regard, the choice of the starting material was crucial, as we aspired for a synthesis that was not only economical but also diversity oriented and readily adaptable to an asymmetric version. After careful scrutiny, the readily available but rarely used, 2,3-dimethyl-2-cyclopentene-1,4-dione **3**[6] was chosen as the launch pad for our projected synthetic efforts toward **1**.

* Corresponding author. Tel.: +91 8022932850; fax: +91 8023600936; e-mail: gm@orgchem.iisc.ernet.in

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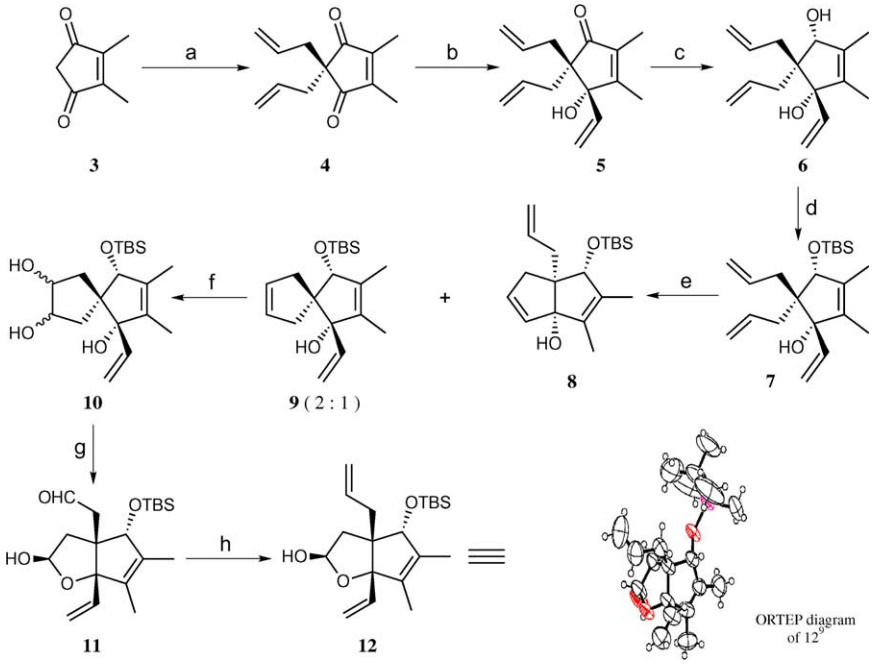
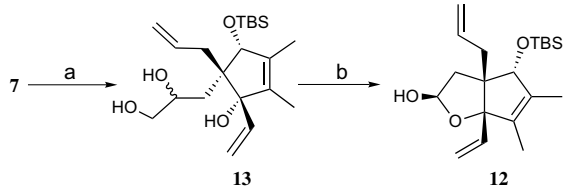



**Scheme 1.** Reagents and conditions: (a) DBU, allyl bromide, THF, 0 °C, 70%; (b) $CeCl_3$, vinyl magnesium bromide, THF, −78 °C, 85%; (c) DIBAL-H, THF, −78 °C, 90%; (d) TBDMSCl, $Et_3N$, rt, 65%; (e) Grubbs catalyst (10 mol%), DCM, rt, 70%; (f) $OsO_4$, NMMO, acetone–water, 0 °C, 85%; (g) $NaIO_4$, THF–water, 0 °C, 90%; (h) $Ph_3PCH_2Br$, $^tBuOK$, 0 °C, 75%.

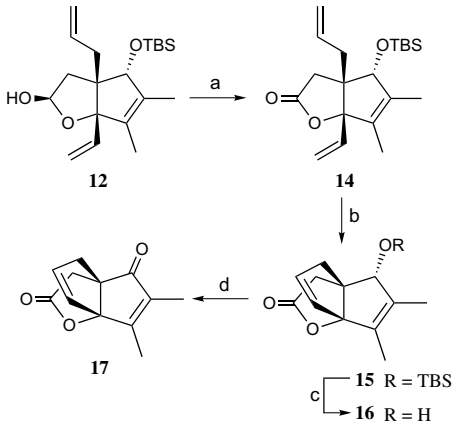
DBU-mediated double allylation of **3** led to the bis-allylated product **4**.[7] Carefully controlled addition of an in situ generated vinylcerium reagent to **4** led to vinyl alcohol **5**,[7] Scheme 1. DIBAL-H reduction of **5** was stereoselective and efficient, with addition from the face opposite to the pre-existing tertiary hydroxy group, to furnish the *cis*-1,3-diol **6**.[7] The secondary hydroxyl group in **6** was readily protected as the TBS derivative **7**. A RCM reaction[8] of **7** led to a readily separable mixture (1:2) of diquinane **8**[7] and the spiro[3.3]nonadiene derivative **9**[7] through the engagement of the allyl–vinyl and allyl–allyl arms, respectively, in the metathetic process, Scheme 1. Regioselective, catalytic $OsO_4$-mediated dihydroxylation of **9** led to **10**[7] and sodium metaperiodate cleavage led to a dialdehyde intermediate, which was concomitantly captured as the lactol **11**,[7] Scheme 1.

Wittig olefination of **11** with the ylide derived from methyltriphenylphosphonium bromide was straightforward and delivered the crystalline **12**[7] and its single crystal X-ray structure determination[9] secured the structural validity of all the compounds prepared thus far in the sequence, Scheme 1. While the desired advanced intermediate **12** could be accessed successfully from **3**, the concurrent formation of the diquinane derivative **8** during the key RCM reaction on **7** was wasteful and required careful chromatographic separation. This minor irritant was circumvented in a simple, but remarkable, way by directly subjecting the tetraene **7** to regioselective, *tert*-hydroxy directed[10] monodihydroxylation of one of the allyl arms with catalytic $OsO_4$, Scheme 2.

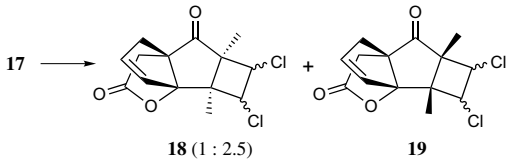
Delightfully, only triol **13** was observed in this reaction and sodium metaperiodate cleavage of the 1,2-diol moiety furnished **12** in excellent yield, Scheme 2. PCC oxidation of **12** was uneventful and cleanly furnished the γ-lactone **14**.[7] A RCM reaction of **14** with the Grubbs first generation catalyst[8] was smooth and delivered **15**, Scheme 3. TBS deprotection of **15** led to the allylic




**Scheme 2.** Reagents and conditions: (a) $OsO_4$, NMMO, acetone–water, 0 °C, 95% based on recovery; (b) $NaIO_4$, THF–water, 0 °C, 90%.




**Scheme 3.** Reagents and conditions: (a) PCC, DCM, rt, 90%; (b) Grubbs catalyst (10 mol%), DCM, rt, 95%; (c) TBAF, 0 °C, quant; (d) $MnO_2$, DCM, rt, 90%.



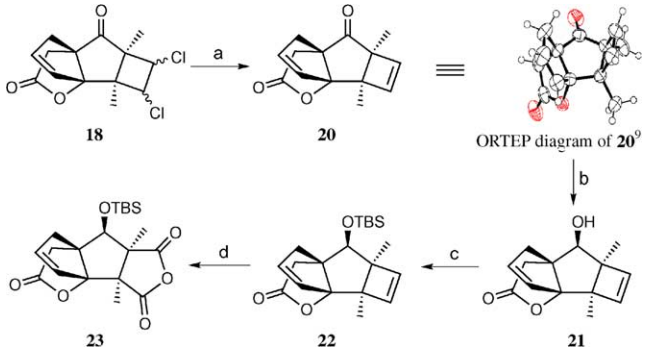

**Scheme 4.** *trans*-1,2-Dichloroethylene, *hv*(pyrex, 400 W), 75%.

alcohol **16** and this was readily oxidized with manganese dioxide to furnish the α,β-unsaturated enone **17**,[7] Scheme 3.

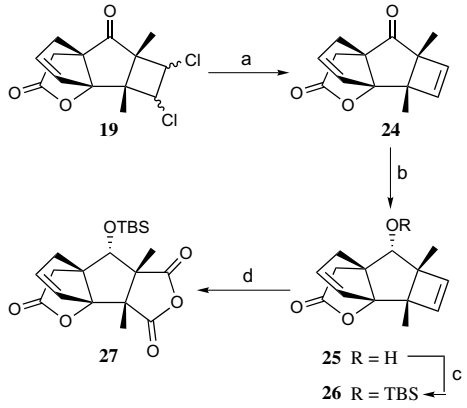
In **17**, the α,β-unsaturated enone functionality had been strategically positioned to install the C5, C6 quaternary carbon centers through a photochemical [2+2]-cycloaddition protocol. Toward this end, a mixture of **17** and an excess of (*E*)-1,2-dichloroethylene was irradiated by a 400 W Hg lamp to furnish a diastereomeric mixture of [2+2]-adducts **18**[7] (1:2.5) and **19**,[7] Scheme 4. Each of the two [2+2]-adducts was also a diastereomeric mixture with respect to the two chlorine substituents present but this was considered inconsequential as eliminative dechlorination was projected as the next step. The observed facial preference for the γ-lactone **17** [2+2] photocycloaddition is not very clear but could be possibly attributed to the ground state through space π–π interaction between the cyclopentene double bond and the enone moiety.

The minor [2+2]-photoadduct **18** on brief exposure to sodium naphthalenide underwent eliminative dehalogenation to furnish the tetracyclic cyclobutene ring bearing compound **20**[7] as a single product and, an X-ray crystal structure determination[9] revealed its stereochemical disposition. In **20**, the two quaternary methyl groups at C5 and C6 were *cis* with respect to the γ-lactone ring as present in the natural product. Reduction of the carbonyl group in **20** was stereoselective with hydride addition from the *exo*-face to deliver **21**[7] with the requisite stereo-disposition of the C7 oxygen functionality. The hydroxyl group in **21** was protected as the TBS derivative **22**[7] and the cyclobutene ring was oxidatively cleaved in a three step sequence involving $OsO_4$-dihydroxylation, metaperiodate cleavage and PCC oxidation to deliver the tetracyclic anhydride **23**[7] and its structure was secured (X-ray), Scheme 5. Tetracyclic compound **23** had the constitution and the key functionalities in the correct stereochemical pattern corresponding to the natural product merrilactone **1**. In addition, the C7 β-hydroxy group in **23** is well poised for the installation of the remaining oxetane ring for which a firmly established precedent already exists.[3,4]

The major [2+2]-photoadduct **19** was also elaborated in a manner identical with its diastereomeric sibling **18**. Thus, sodium naphthalenide mediated dechlorination to **24**[7] and stereoselective hydride reduction furnished the tetracyclic compound **25**,[7] Scheme 6. TBS protection of the hydroxyl group to **26** and a three step oxidative cleavage of the cyclobutene ring eventuated in the tetracyclic anhydride **27**,[7] Scheme 6.




**Scheme 5.** Reagents and conditions: (a) Na-naphthalenide, −60 °C, 35%; (b) $NaBH_4$, 0 °C, 99%; (c) TBDMSCl, $Et_3N$, 85 °C, 85%; (d) (i) $OsO_4$, NMMO, acetone–water, 0 °C, (ii) $NaIO_4$, THF–water; (iii) PCC, DCM, rt (45% over three steps).




**Scheme 6.** Reagents and conditions: (a) Na-naphthalenide, −60 °C, 35%; (b) $NaBH_4$, 0 °C, 99%; (c) TBDMSCl, $Et_3N$, 85 °C, 85%; (d) (i) $OsO_4$, NMMO, acetone–water, 0 °C, (ii) $NaIO_4$, THF–water, (iii) PCC, DCM, rt (60% over three steps).

In short, we have delineated a new synthetic approach toward the neurotrophic factor merrilactone A **1** from the readily available precursor 2,3-dimethyl-2-cyclopentene-1,4-dione. In a relatively short sequence, the core structural motif present in this sesquiterpenoid has been realized through a series of stereoselective steps, setting the stage for the synthesis of the natural product and its analogues.

## Acknowledgements

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7. All new compounds were fully characterized on the basis of spectral data (IR, $^1$H, $^{13}$C NMR, and HRMS). Selected spectral data: Compound **17**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.06–5.96 (m, 2H), 2.96 (1/2ABq, $J$ = 19.2 Hz, 1H), 2.86 (dt, $J$ = 18.6, 2.4 Hz, 1H), 2.78 (1/2ABq, $J$ = 18.9 Hz, 1H), 2.65 (dt, $J$ = 18.9, 2.4 Hz, 1H), 2.15 (s, 3H), 1.74 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): 205.7, 174.6, 165.3, 138.2, 137.1, 127.6, 104.1, 55.6, 41.7, 39.3, 12.9, 8.2; HRMS (ES) *m*/*z* calcd for $C_{12}H_{12}NaO_3$, $[M+Na]^+$: 227.0684, found 227.0688. Compound **20**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.24 (d, $J$ = 3.0 Hz, 1H), 6.02 (d, $J$ = 2.4 Hz, 1H), 6.01–5.99 (m, 1H), 5.89–5.85 (m, 1H), 3.10 (1/2ABq, $J$ = 18.3 Hz, 1H), 2.63 (dd as t, $J$ = 2.1 Hz, 2H), 2.48 (1/2ABq, $J$ = 18.6 Hz, 1H), 1.34 (s, 3H), 1.20 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 216.2, 174.4, 144.1, 139.0, 132.0, 130.4, 102.3, 66.2, 62.8, 56.3, 44.8, 40.7, 14.3, 13.3; HRMS (ES) *m*/*z* calcd for $C_{14}H_{14}NaO_3$, $[M+Na]^+$: 253.0841, found 253.0848. Compound **22**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.06 (d, $J$ = 2.7 Hz, 1H), 5.89 (d, $J$ = 3 Hz, 1H), 5.83 (s, 2H), 3.77 (s, 2H), 2.76 (d, $J$ = 16.8 Hz, 1H), 2.74 (d, $J$ = 18.0 Hz, 1H), 2.40 (d, $J$ = 17.4 Hz, 1H), 2.08 (d, $J$ = 17.4 Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 176.1, 139.6, 138.0, 133.5, 130.9, 105.0, 82.9, 63.1, 61.3, 56.8, 45.4, 40.2, 25.7 (3C), 19.1, 18.1, 14.2, −4.1, −4.6; HRMS (ES) *m*/*z* calcd for $C_{20}H_{30}O_3Si$, $[M+H]^+$: 347.2042, found 347.2031. Compound **23**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.04–6.02 (m, 1H), 5.94–5.92 (m, 1H), 4.00 (s, 1H), 3.05 (dt, $J$ = 18.3, 2.1 Hz, 1H), 2.84 (1/2ABq, $J$ = 18.6 Hz, 1H), 2.70 (1/2ABq, $J$ = 18.6 Hz, 1H), 2.21 (dt, $J$ = 18.0, 2.1 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 173.8, 171.8, 170.6, 136.3, 130.0, 106.6, 85.6, 61.9, 60.0, 59.7, 44.4, 39.8, 25.5 (3C), 17.9, 15.0, −4.3, −4.9; HRMS (ES) *m*/*z* calcd for $C_{20}H_{28}NaO_6Si$, $[M+Na]^+$: 415.1553, found 415.1568. Compound **24**: $^1$H NMR (300 MHz, $CDCl_3$):$\delta$ 6.55 (d, $J$ = 2.7 Hz, 1H), 6.16 (d, $J$ = 2.7 Hz, 1H), 6.12–6.09 (m, 1H), 5.91–5.88 (m, 1H), 3.12 (dt, $J$ = 18.3, 1.8 Hz, 1H), 3.00 (1/2ABq, $J$ = 18.6 Hz, 1H), 2.81 (1/2ABq, $J$ = 18.9 Hz, 1H), 2.55 (dt, $J$ = 18.3, 2.1 Hz, 1H), 1.34 (s, 3H), 1.15 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 215.0, 174.9, 144.7, 140.3, 138.4, 128.7, 102.2, 65.6, 59.8, 57.3, 45.8, 42.9, 15.8, 12.9; HRMS (ES) *m*/*z* calcd for $C_{14}H_{14}NaO_3$, $[M+Na]^+$: 253.0841; found 253.0840. Compound **26**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.24 (d, $J$ = 2.7 Hz, 1H), 6.21 (d, $J$ = 3.0 Hz, 1H), 6.08–6.06 (m, 1H), 5.87–5.85 (m, 1H), 3.52 (s, 1H), 3.29 (d, $J$ = 18.6, 1H), 2.75 (d, $J$ = 17.4 Hz, 1H), 2.40 (d, $J$ = 17.4 Hz, 1H), 2.31 (d, $J$ = 18.3 Hz, 1H), 1.16 (s, 3H), 1.05 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.6, 142.0, 139.6, 137.8, 130.1, 104.3, 84.2, 61.3, 58.0, 57.6, 49.4, 39.1, 25.7 (3C), 18.7, 18.1, 15.9, −4.2, −4.7; HRMS (ES) *m*/*z* calcd for $C_{20}H_{30}O_3Si$, $[M+H]^+$: 347.2042, found 347.2036.
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9. Crystal data for compound **12**: Crystal system: Monoclinic, space group: $P2_1/c$, cell parameters: $a$ = 12.633(3) Å, $b$ = 13.361(3) Å, $c$ = 13.8096(32) Å, $\beta$ = 107.281(4)°, $V$ = 2225.66 Å$^3$, $Z$ = 4, $\rho$(cald) = 1.308 g cm$^{-3}$, $F$(0 0 0) = 960.0, $\mu$ = 0.12 mm$^{-1}$, $\lambda$ = 0.71073 Å. $R1$ = 0.1206 for 2976 $F_o > 2\sigma(F_o)$ and 0.1411 for all 3916 data. $wR2$ = 0.3676, GooF = 1.456. Crystal data for compound **20**: Crystal system: Triclinic, space group: $P$-1, cell parameters: $a$ = 7.254(5) Å, $b$ = 8.124(5) Å, $c$ = 11.459(7) Å, $\alpha$ = 105.21(1)°, $\beta$ = 90.79(1)°, $\gamma$ = 114.36(1)°, $V$ = 587.9 Å$^3$, $Z$ = 2, $\rho$(cald) = 1.301 g cm$^{-3}$, $F$(0 0 0) = 244.0, $\mu$ = 0.09 mm$^{-1}$, $\lambda$ = 0.71073 Å. $R1$ = 0.0464 for 1725 $F_o > 2\sigma(7F_o)$ and 0.0579 for all 2062 data. $wR2$ = 0.1097, GooF = 1.061. All ORTEP diagrams have been drawn with 50% ellipsoidal probability. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, [CCDC 254396 for **12** and CCDC 254397 for **20**]. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; email:deposit@ccdc.cam.ac.uk.
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