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Total synthesis of (±)-bruguierol A via an intramolecular [3+2] cycloaddition of cyclopropane 1,1-diester

Bao Hu, Siyang Xing, Jun Ren, Zhongwen Wang *

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

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ABSTRACT

Total synthesis of natural product (±)-bruguierol A was accomplished in 10-steps and with an overall 16.8% yield. The embedded unique 8-oxabicyclo[3.2.1]octane core skeleton in this natural product was constructed via a novel $Sc(OTf)_3$-catalyzed intramolecular [3+2] cycloaddition of cyclopropane, which was developed recently in this laboratory. This general synthetic strategy can be potentially applied to the synthesis of a broad range of structurally related natural products.

1. Introduction

Bruguierols A–C (Fig. 1) were isolated and characterized by Sattler and co-workers from the stem of *Bruguiera gymnorrhiza* tree in 2005.[1] These natural products have the unique structure characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. With the interesting structural features and potential biological activities, synthesis of bruguierols began to attract attention from the synthetic community.[2] Up to now, there are four synthetic routes reported for the total synthesis of bruguierols. In 2007, Ramana and co-workers[2a] reported the application of [2+2+2] alkyne cyclotrimerisation as the key step for the construction of benzannulated 8-oxabicyclo[3.2.1]octane skeleton to complete the total synthesis of bruguierol A. Wu and co-workers[2b] have completed the total synthesis of racemic bruguierol A in 2008. The key bridged cyclic framework was constructed using an intramolecular Friedel–Crafts alkylation with a ketal as the alkylating agent developed in their group several years ago.[3] A similar total synthesis of (+)-bruguierol C was also presented by Jennings and Solorio[2c] Recently, Fañanás and co-workers have applied an efficient tandem intramolecular hydroalkoxylation/hydroarylation reaction for the construction of the key bridged cyclic framework to the total synthesis of bruguierol A.[2d]

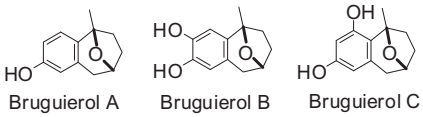

Figure 1. Bruguierols A–C.

Recently, we have developed a general strategy for efficient construction of bridged oxa- and aza-[n.2.1] skeletons via a Lewis acid-catalyzed intramolecular [3+2] cycloaddition of cyclopropane 1,1-diesters with carbonyls and imines, and successfully applied it to the synthesis of platensimycin.[4] In this paper, we wish to report the application of this strategy to the total synthesis of (±)-bruguierol A (**1**).

2. Results and discussion

Retrosynthetic analysis of (±)-bruguierol A (**1**) is shown in Scheme 1. We envisioned that compound (±)-**1** could be synthesized by decarboxylation and demethylation of an intermediate **2**. The key step is the construction of the 8-oxabicyclo[3.2.1]octane skeleton in **2** by an intramolecular [3+2] cycloaddition of cyclopropane **3**,[4] which could be readily synthesized from commercially available 3-bromoanisole.

* Corresponding author. Tel.: +86 22 23498191; e-mail address: wzwrj@nankai.edu.cn (Z. Wang).
URL: http://wzw.nankai.edu.cn

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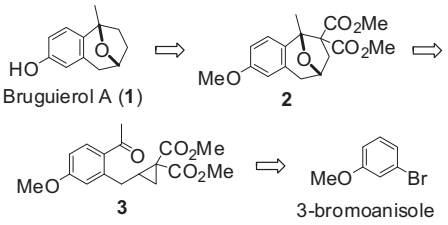
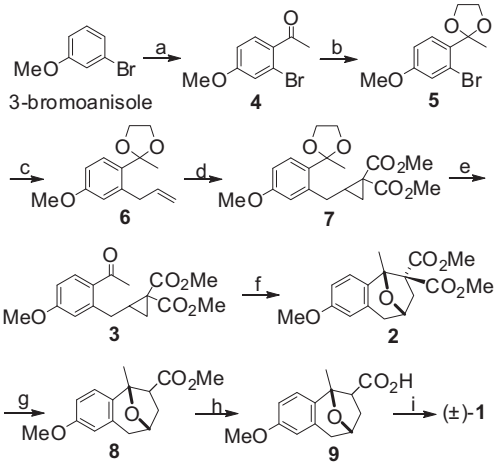


Scheme 1. Retrosynthetic analysis of **1**.

With the initial blueprint in mind, we started the synthesis of bruguierol A as depicted in Scheme 2. Friedel–Crafts acylation of 3-bromoanisole afforded compound **4** in 72% yield.[5] Protection of acetophenone **4** gave ketal **5**.[6] Allylation of **5** using a Grignard reagent only gave 20% yield of **6**. A halogen/lithium exchange method was applied successfully and compound **6** was obtained in 64% yield.[7] Cyclopropanation of **6** with diazodimethyl-malonate in the presence of $Rh_2(OAc)_4$ afforded cyclopropane **7** in a poor yield (35%), together with a certain amount of recovered starting material. Fortunately, when $Rh_2(esp)_2$ was used as the catalyst, the yield of **7** was improved to 77%.[8] Deprotection of the ketal **7** with 10% HCl in THF was successfully carried out (95%) and the product ketone **3** was implemented to the subsequent reaction without further purification. The 8-oxabicyclo[3.2.1]octane core skeleton could be easily constructed by a $Sc(OTf)_3$-catalyzed intramolecular [3+2] cycloaddition recently developed in our labarotary,[4] and the key intermediate **2** was almost quantitatively obtained. Attempts to prepare carboxylic acid **9** by hydrolyzation and decarboxylation of the germinal diesters in **2** under acidic conditions proved to be unsuccessful.[9] Fortunately, Krapcho decarboxylation[10] of **2** was successfully carried out to afford the corresponding monoester **8** (88%), which was then saponified to afford carboxylic acid **9** in 88% yield. It should be noted that the Krapcho decarboxylation of **2** almost exclusively gave the single isomer **8**. We proposed that the stereochemistry of **8** is *endo* as showed in the synthesis of platensimycin.[4] Finally, the total synthesis of (±)-bruguierol A was achieved after the Barton decarboxylation[11] and demethylation[2b,12] of **9**. The spectrum data were identical to those reported in the literature.[2a,b,d]



Scheme 2. Synthesis of (±)-bruguierol A. Reagents and conditions: (a) $AlCl_3$, CH_3COCl, 72%; (b) *p*-TsOH, ethylene glycol, 94%; (c) *t*-BuLi, Et_2O, allyl bromide, 64%; (d) $N_2{=}C(CO_2Me)_2$, $Rh_2(esp)_2$, 77%; (e) 1 M HCl, THF, room temperature, 95%; (f) $Sc(OTf)_3$, DCE, 98%; (g) LiCl, wet DMSO, 160 °C, 88%; (h) LiOH, MeOH, H_2O, THF, 88%; (i) (1) Barton decarboxylation, then (2) NaSEt, DMF, 70% (two steps).

3. Conclusions

In summary, a total synthesis of (±)-bruguierol A was successfully accomplished from commercially available 3-bromoanisole in 10-steps and with an overall 16.8% yield. The key step, a $Sc(OTf)_3$-catalyzed intramolecular [3+2] cycloaddition of cyclopropane **3** was employed for efficient construction of the 8-oxabicyclo[3.2.1] octane core skeleton. This synthetic strategy also provides a general protocol for synthesis of other structurally related natural and unnatural products.

4. Experimental section

4.1. General method

All NMR spectra were recorded with a spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in $CDCl_3$. The chemical shifts were reported in parts per million referenced to $CDCl_3$ (δ=7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0 ppm) for ^{13}C NMR spectroscopy. Column chromatography was performed on silica gel (100–200 or 200–300 mesh) using petroleum ether and EtOAc as eluent. Thin layer chromatography (TLC) was performed on Merck silica gel GF_{254} plates and visualized by UV light (254 nm). Melting points were uncorrected. All solvents were purified and dried using standard procedures. Abbreviations: AIBN=2,2′-azobisisobutyronitrile, DCE=1,1-dichloroethane, DCM=dichloromethane, DMAP=*N*,*N*-dimethylaminopyridine, DMF=*N*,*N*-dimethylformamide, DMSO=dimethylsulfoxide, esp=a,a,a′,a′-tetramethyl-1,3-benzenedipropanoate, THF=tetrahydrofuran, Ts=*p*-toluenesulfonyl.

*4.1.1. 2-Bromo-3-methoxyacetophenone (**4**).* Under an argon atmosphere, a mixture of 3-bromoanisole (37.4 g, 0.2 mol), anhydrous $AlCl_3$ (32.0 g, 0.24 mol, 1.2 equiv), and 200 mL of dry CH_2Cl_2 was cooled below 5 °C with an ice-bath, and acetyl chloride (15.8 g, 14.4 mL, 0.2 mol, 1.2 equiv) was added dropwise. The mixture was allowed to reach room temperature and stirred overnight, then poured into 250 mL of ice-water containing 40 mL of concentrated HCl and stirred to reach room temperature. The organic phase was separated, and the aqueous layer was washed with CH_2Cl_2 (40 mL×3). The combined organic phase was washed with H_2O (20 mL×3), 10% aqueous NaOH (20 mL×3), H_2O (20 mL×3), and brine (20 mL×3), dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was distilled at 116–120 °C (1 mmHg) to afford the product **4** (33.08 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.16 (d, *J*=2.0 Hz, 1H, Ar*H*), 6.89 (dd, *J*=2.0, 8.4 Hz, 1H, Ar*H*), 3.85 (s, 3H, OCH_3), 2.64 (s, 3H, CH_3).

*4.1.2. 2-(2-Bromo-4-methoxyphenyl)-2-methyl-1,3-dioxolane (**5**).* To a solution of 2-bromo-3-methoxyacetophenone (29.19 g, 0.13 mol) in toluene (250 mL) at 25 °C was added ethylene glycol (11.79 g, 0.19 mol, 1.5 equiv) and *p*-TsOH (1.24 g, 6.5 mmol, 5 mol %). The solution was refluxed overnight with a Dean/Stark trap. An additional 2 equiv (16.14 g, 0.26 mol) of ethylene glycol was added in two equal portions and the solution was unceasingly heated at reflux for 1 day. The toluene solution was cooled to 25 °C, water (200 mL) was added followed by extraction with EtOAc (100 mL×3). The combined organic layers were washed with H_2O (200 mL×3) and brine (200 mL×2), dried over $MgSO_4$, and then concentrated on a rotary evaporator. The desired product **5** (33.27 g, 94%) was isolated as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J*=8.8 Hz, 1H, Ar*H*), 6.96 (d, *J*=2.4 Hz, 1H, Ar*H*), 6.62 (dd, *J*=2.4, 8.8 Hz, 1H, Ar*H*), 3.86 (t, *J*=6.8 Hz, 2H, CH_2), 3.61 (s, 3H, OCH_3), 3.56 (t, *J*=6.8 Hz, 2H, CH_2), 1.60 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 133.1, 128.7, 120.9, 120.1, 112.7, 108.6, 64.2, 55.5, 25.5; IR

(thin film): ν=2987, 2939, 2889, 1601, 1486, 1292, 1239, 1197, 1038, 1021 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}BrO_3H$ $(M+H)^+$: 273.0121; found: 273.0127.

*4.1.3. 2-(2-Allyl-4-methoxyphenyl)-2-methyl-1,3-dioxolane (**6**).* *Method A*: Under an argon atmosphere, ketal **5** (2.73 g, 10 mmol) was dissolved in 20 mL of diethyl ether, and the solution was cooled to −80 °C. To the mixture was slowly added 9.2 mL of *tert*-butyllithium (12 mmol, 1.3 M in pentane). After stirring for 2 h, 2.5 mL of 3-bromopropene (30 mmol, 3.0 equiv) was added. The reaction mixture was warmed slowly to room temperature and stirred overnight prior to being quenched with saturated NH_4Cl solution. The product was extracted into portions of ether (20 mL×3). The combined organic phases were washed with H_2O (20 mL×2) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=20:1 to 10:1) to afford 1.48 g (63%) of alkene **6** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J=8.4 Hz, 1H, Ar*H*), 6.76 (d, J=2.4 Hz, 1H, Ar*H*), 6.71 (dd, J=2.4, 8.4 Hz, 1H, Ar*H*), 6.04–5.91 (m, 1H, CH_2=C*H*), 5.08 (d, J=5.2 Hz, 1H, CH_2=CH), 5.04 (s, 1H, CH_2=CH), 4.05–3.98 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.76–3.71 (m, 2H, CH_2), 3.63 (d, J=6.4 Hz, 2H, CH_2), 1.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 139.2, 138.2, 132.6, 127.6, 116.7, 115.6, 110.8, 109.3, 64.1, 55.2, 37.4, 27.6; IR (thin film): ν=2988, 2953, 2889, 1607, 1246, 1192, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_3H$ $(M+H)^+$: 235.1329; found: 235.1336.

Method B: Under an argon atmosphere, 3-bromopropene (1.27 mL, 15 mmol, 1.5 equiv) was added to a solution of the Grignard reagent prepared by adding a solution of ketal **5** (2.73 g, 10 mmol) in THF (30 mL) to a suspension of magnesium powder (0.288 g, 12 mmol, 1.2 equiv) and I_2 in THF (10 mL). The reaction mixture was refluxed for 1 h, cooled, and quenched with a saturated solution of NH_4Cl. After being diluted with H_2O (30 mL), the mixture was extracted with ether (20 mL×3). The combined extracts were washed with H_2O (20 mL×2) and brine (10 mL), dried over Na_2SO_4, and concentrated to a residue. The residue was subsequently purified by flash column chromatography on silica gel to give 0.471 g (20%) of the desired product **6**, which was identical to that prepared by method A.

*4.1.4. Dimethyl 2-(5-methoxy-2-(2-methyl-1,3-dioxolan-2-yl)benzyl) cyclopropane-1,1-dicarboxylate (**7**). Method A*: Under an argon atmosphere, $Rh_2(esp)_2$ (4 mg, 5 μmol, 0.1 mol %) and 5 mL of CH_2Cl_2 were placed in a 50-mL three-necked flask equipped with a magnetic stir bar. The compound **6** (1.171 g, 5 mmol, 1 equiv) was added and the reaction mixture was then cooled to below 3 °C in a water/ice bath. After 5 min, a solution of diazodimethylmalonate (1.028 g, 6.5 mmol, 1.3 equiv) in CH_2Cl_2 (5.0 mL) was added by syringe pump (1.5 mL/hr). The resulting solution was kept in the bath for 10 min and then stirred overnight. After being cooled to room temperature, the mixture was concentrated. The residue was then purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10:1 to 5:1) to afford 1.408 g (77%) of the desired product **7** as a white solid. Mp 72–73 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J=8.4 Hz, 1H, Ar*H*), 6.87 (d, J=2.4 Hz, 1H, Ar*H*), 6.71 (dd, J=2.4, 8.4 Hz, 1H, Ar*H*), 4.01 (t, J=6.4 Hz, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.71 (t, J=6.4 Hz, 2H, OCH_2), 3.12 (dd, J=5.6, 15.2 Hz, 1H, ArCH_2), 2.66 (dd, J=8.4, 15.2 Hz, 1H, ArCH_2), 2.13–2.18 (m, 1H, C*H*-cyclopropane), 1.66 (dd, J=5.6, 8.0 Hz, 1H, CH_2-cyclopropane), 1.62 (s, 3H, CH_3), 1.50 (dd, J=4.8, 9.2 Hz, 1H, CH_2-cyclopropane); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 168.7, 159.2, 138.9, 132.8, 127.6, 115.8, 111.0, 109.2, 64.1, 64.0, 55.2, 52.7, 52.6, 34.3, 31.3, 29.2, 27.5, 21.6; IR (KBr): ν=2993, 2956, 2898, 1736, 1723, 1322, 1276, 1214, 1137, 1034, 824 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}O_7Na$ $(M+Na)^+$: 387.1414; found: 387.1414.

Method B: Under an argon atmosphere, a solution of dimethyl diazomalonate (1.151 g, 7.28 mmol, 1.1 equiv) in CH_2Cl_2 (28 mL) was added via syringe pump (2 mL/hr) to a refluxing solution of $Rh_2(OAc)_4$ (14.6 mg, 33 μmol, 0.5 mol %) and the alkene **6** (1.55 g, 6.62 mmol, 1 equiv) in CH_2Cl_2 (20 mL). The reaction mixture was then refluxed for 23 h. After being cooled to room temperature, the mixture was concentrated. The residue was purified by column chromatography on silica gel, then was recrystallized to afford the desired product **7** (0.847 g, 35%), which was identical to that prepared by method A.

*4.1.5. Dimethyl 2-(2-acetyl-5-methoxybenzyl)cyclopropane-1,1-dicarboxylate (**3**).* To a solution of ketal **7** (796 mg, 2.2 mmol) in THF (20 mL) was slowly added 5.7 mL of 1 M HCl (5.7 mmol, 2.6 equiv) below 10 °C. The reaction solution was stirred overnight at room temperature. Then saturated NH_4Cl solution was added and extracted with ether (20 mL×3). The combined organic phases were washed with H_2O (20 mL×2) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The ketone **3** (671 mg, 95%) was obtained as a white solid, which was not purified further and was used directly in the next step. Mp 86–87 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J=8.4 Hz, 1H, Ar*H*), 6.82 (s, 1H, Ar*H*), 6.80 (d, J=8.8 Hz, 1H, Ar*H*), 3.85 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 3.71 (s, 3H, CO_2CH_3), 3.20 (dd, J=6.4, 14.8 Hz, 1H, ArCH_2), 2.85 (dd, J=7.6, 14.8 Hz, 1H, ArCH_2), 2.55 (s, 3H, COCH_3), 2.37–2.22 (m, 1H, C*H*-cyclopropane), 1.64–1.53 (m, 1H, CH_2-cyclopropane), 1.44 (dd, J=4.8, 9.2 Hz, 1H, CH_2-cyclopropane); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 170.5, 168.6, 162.2, 143.4, 132.9, 129.3, 116.5, 110.9, 55.3, 52.6, 52.5, 34.2, 32.9, 29.1, 28.1, 21.1; IR (KBr): ν=2961, 2938, 1772, 1670, 1436, 1321, 1291, 1249, 1212, 1134, 1066 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}O_6Na$ $(M+Na)^+$: 343.1153; found: 343.1152.

*4.1.6. 5-Methoxyl-1-methyl-12-oxatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-triene-11,11-dicarboxylic acid dimethyl ester (**2**).* Ketone **3** (602 mg, 1.9 mmol) was dissolved in 15 mL DCE, 185 mg of $Sc(OTf)_3$ (0.38 mmol, 20 mol %) was added to the solution at room temperature under an argon atmosphere. The reaction mixture was stirred overnight. After filtration through Celite, the organics were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5:1) to afford 590 mg (98%) of the desired product **2** as a white solid. Mp 88–89 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J=8.4 Hz, 1H, Ar*H*), 6.65 (dd, J=2.4, 8.8 Hz, 1H, Ar*H*), 6.56 (d, J=2.4 Hz, 1H, Ar*H*), 4.81–4.73 (m, 1H, OC*H*), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, CO_2CH_3), 3.54 (s, 3H, CO_2CH_3), 3.36 (dd, J=4.8, 16.4 Hz, 1H, ArCH_2), 2.79 (dd, J=8.0, 13.6 Hz, 1H, ArCH_2), 2.59 (d, J=16.8 Hz, 1H, CH_2), 2.47 (dd, J=2.4, 13.6 Hz, 1H, CH_2), 1.86 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 169.0, 159.0, 133.6, 131.8, 127.6, 113.6, 111.5, 83.8, 72.7, 70.9, 55.1, 52.7, 52.4, 38.7, 37.3, 20.9; IR (KBr): ν=2953, 1745, 1720, 1247, 1082, cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}O_6Na$ $(M+Na)^+$: 343.1153; found: 343.1152.

*4.1.7. 5-Methoxyl-1-methyl-12-oxatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-triene-11-carboxylic acid methyl ester (**8**).* Diester **2** (358 mg, 1.11 mmol) and lithium chloride (474 mg, 11.14 mmol, 10.0 equiv) were dissolved in wet DMSO (15 mL) and heated to 160 °C for 4 h. The solution was cooled to room temperature, diluted with 50 mL of water and extracted with EtOAc (15 mL×3). The organic layers were combined and washed with brine (20 mL×2), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=10:1 to 5:1). Monoester **8** (256 mg, 88%) was obtained as a colorless oil and as a single *endo* diastereoisomer; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.93 (d, J=8.4 Hz, 1H, Ar*H*), 6.63 (d,

J=2.4 Hz, 1H, ArH), 6.61 (s, 1H, ArH), 4.70 (t, J=6.0 Hz, 1H, OCH), 3.75 (s, 3H, OCH_3), 3.49 (s, 3H, CO_2CH_3), 3.37 (dd, J=5.2, 16.4 Hz, 1H, CHCO$_2$Me), 3.06 (dd, J=6.8, 10.8 Hz, 1H, ArCH_2), 2.59 (d, J=16.4 Hz, 1H, ArCH_2), 2.50–2.37 (m, 1H, CH_2), 2.30–2.19 (m, 1H, CH_2), 1.86 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 158.7, 133.6, 131.7, 124.8, 114.0, 111.4, 81.8, 73.7, 58.7, 55.1, 51.8, 37.2, 33.3, 23.1; HRMS (ESI) calcd for $C_{15}H_{18}O_4Na$ $(M+Na)^+$: 285.1097; found: 285.1105.

*4.1.8. 5-Methoxyl-1-methyl-12-oxatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-triene-11-carboxylic acid (**9**).* A solution of monoester **8** (256 mg, 0.98 mmol) was dissolved in MeOH (20 mL) and water (20 mL), and to this solution LiOH/H_2O (410 mg, 9.8 mmol, 10 equiv) was added. The mixture was stirred at room temperature for 17.5 h. The MeOH was evaporated, and the aqueous mixture was acidified by a careful addition of 1 M HCl to adjust the pH value to 2–3. NaCl was added to saturate the aqueous solution which was then extracted with ether (15 mL×5). The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated to afford carboxylic acid **9** (214 mg, 88%) as a white solid, which was used in the subsequent transformation without further purification. Mp 153–154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.99 (d, J=9.2 Hz, 1H, ArH), 6.61 (s, 2H, ArH), 4.71 (t, J=6.0 Hz, 1H, OCH), 3.76 (s, 3H, OCH_3), 3.37 (dd, J=4.8, 16.4 Hz, 1H, CHCO$_2$H), 3.07 (dd, J=7.2, 10.8 Hz, 1H, ArCH_2), 2.59 (d, J=16.8 Hz, 1H, ArCH_2), 2.50–2.38 (m, 1H, CH_2), 2.15 (dd, J=7.2, 12.8 Hz, 1H, CH_2), 1.85 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3, 158.8, 133.4, 131.2, 125.4, 113.9, 111.5, 81.9, 73.6, 58.7, 55.1, 37.2, 32.9, 22.9; IR (KBr): ν=2997, 2957, 1728, 1613, 1502, 1252, 1205, 1109, 1032, 1016 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}O_4Na$ $(M+Na)^+$: 271.0941; found: 271.0944.

*4.1.9. (±)-Bruguierol A (**1**).* A solution of carboxylic acid **9** (214 mg, 0.86 mmol) in CH_2Cl_2 (20 mL) was treated at 10 °C with DMF (two drop) and oxalyl chloride (888 mg, 0.60 mL, 7.00 mmol, 8.0 equiv). The reaction mixture was warmed to room temperature and stirred for 2 h, after which all volatiles were removed in vacuo. The crude acyl chloride was redissolved in THF (20 mL) at room temperature in a round-bottom flask shielded from light with aluminum foil. With stirring, 2-mercaptopyridine *N*-oxide sodium salt (207 mg, 1.39 mmol, 1.6 equiv) and DMAP (21 mg, 0.17 mmol, 20 mol %) were added to the above solution, and the mixture was stirred in the dark for 2 h. Upon completion, the solvent was evaporated. To a solution of the residue in benzene (30 mL) were added Bu_3SnH (751 mg, 0.70 mL, 2.58 mmol, 3.0 equiv) and AIBN (22 mg, 0.16 mmol, 18 mol %), and the mixture was heated to reflux with vigorous stir for 4 h. Additional Bu_3SnH (250 mg, 0.23 mL, 0.86 mmol, 1.0 equiv) and AIBN (15 mg, 0.09 mmol, 10 mol %) were added to the reaction mixture, which was kept at reflux overnight. After being cooled to room temperature, the mixture was treated with saturated aqueous NH_4Cl solution (20 mL) and vigorously stirred for an additional 1 h. The organic layer was separated. The water layer was extracted with ether (20 mL×2). The combined organic phases were washed with H_2O (20 mL×2) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel to obtain crude Barton decarboxylation product as a yellow oil, which was used for the next step without further purification.

Under an argon atmosphere, a 100 mL three-necked round-bottom flask was charged with NaH (60% in mineral oil, 826 mg, 21 mmol) and washed with petroleum ether for several times to remove mineral oil. DMF (25 mL) and ethanethiol (1.07 g, 1.5 mL, 20 mmol) were added, and the slurry was stirred for 1.5 h. To this slurry, a solution of the above Barton decarboxylation product in DMF (15 mL) was added, and the mixture was heated to 150 °C for 45 h. After being cooled to room temperature, the mixture was acidified with 1 N HCl (5 mL) and extracted with Et_2O (5 mL×3). The combined organic layers were washed successively with water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=1:10 to 1:5) to yield 115 mg (two steps, 70%) of pure compound (±)-**1** (Bruguierol A) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 7.08 (br s, 1H), 6.89 (d, J=8.4 Hz, 1H), 6.51 (dd, J=8.4, 2.4 Hz, 1H), 6.38 (d, J=2.4 Hz, 1H), 4.65 (t, J=6.0 Hz, 1H), 3.17 (dd, J=16.8, 5.2 Hz, 1H), 2.31 (d, J=16.8 Hz, 1H), 2.23–2.10 (m, 1H), 1.97–1.87 (m, 1H), 1.84–1.71 (m, 1H), 1.69–1.55 (m, 1H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9, 135.5, 133.2, 124.0, 115.8, 113.2, 81.0, 74.5, 42.9, 37.5, 30.4, 22.8; IR (thin film): ν=3303, 2975, 1611, 1584, 1499, 1456, 1287, 1261, 1236, 1090, 1030, 994, 858, 816 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}O_2$ $(M-H)^-$: 189.0921; found: 189.0926.

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Supplementary data

Electronic Supplementary data (ESI) copies of ^{1}H and ^{13}C NMR spectra are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.05.057. These data include MOL files and InChIKeys of the most important compounds described in this article.

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