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Enantioselective Total Synthesis of Briarellins E and F: The First Total Syntheses of Briarellin Diterpenes

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Marine invertebrates continue to serve as invaluable repositories of structurally novel and biologically active secondary metabolites.[1] In particular, a striking diversity of diterpene cyclic ethers has been isolated from soft corals and gorgonian octocorals.[2] The cladiellins (e.g., **1**−**3**), briarellins (e.g., **4** and **5**), and asbestinins (e.g., **6**) belong to the C2,C11-cyclized cembranoid diterpene family[2] and have in common a rare oxatricyclic ring system as well as six stereogenic centers (carbons 1−3, 9, 10, and 14).[3] Although the natural role of these oxacyclic diterpenes is believed to be predation deterrence,[2,4] they also display interesting activity in human cell assays;[2] for example, briarellin diterpenes have recently been shown to be active against the malaria parasite *Plasmodium falciparum*.[5] Briarellins E (**4**) and F (**5**), like most briarellin diterpenes,[3] were isolated by Rodríguez and co-workers from Caribbean gorgonian octocorals belonging to the genus *Briareum*.[5,6] The constitution and relative configuration of these diterpenes were established on the basis of NMR studies and chemical correlations. Herein we report asymmetric total syntheses of briarellins E (**4**) and F (**5**). These first total syntheses of briarellin diterpenes confirm the structure assignments for **4** and **5** and establish their absolute configurations.

Our plan for preparing briarellins E (**4**) and F (**5**) was based on chemistry we developed recently for the total synthesis of cladiellin diterpenes.[7] We foresaw these briarellin diterpenes evolving from a formyl tetrahydroisobenzofuran **7** that, in the central strategic step of the synthesis, would be formed by Prins-pinacol condensation of a (*Z*)-α,*β*-unsaturated aldehyde **8** and an (*S*)-carvone-derived alkynyl dienyl diol **9** (Scheme 1). Stereoselective trans dihydroxylation of the (*Z*)-1-methyl-1-butenyl side chain of **7**[7e] would allow elaboration of the oxepane ring and installation of the α C4 caprylate substituent of **4**, whereas regio- and stereoselective hydration of the cyclohexene moiety would introduce the *β* C11 hydroxyl group. As in our earlier syntheses of cladiellin diterpenes,[7] the bridging nine-membered ring was to be formed at a late stage by Nozaki−Hiyama−Kishi ring closure.[8]

The syntheses commenced by preparing an appropriately substituted cyclohexadienyl diol for use in the Prins-pinacol reaction (Scheme 2). Protonolysis of the silyl ketene acetal derived from bicyclic lactone **10**[9,10] with AcOH, followed by reduction with $LiAlH_4$ provided diol **11**.[11] Selective protection of the primary alcohol of **11** as a TIPS ether and subsequent oxidation of the secondary alcohol with PCC/NaOAc[12] gave enone **12**. Conversion of **12** to the corresponding kinetic enol triflate[13] using LDA and 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine,[14] followed by palladium-catalyzed coupling with $(Me_3Sn)_2$[15] and in situ iodination of the resulting vinylstannane with *N*-iodosuccinimide (NIS)[16] delivered cyclohexadienyl iodide **13**. Coupling of α-alkoxy aldehyde **14**[7b] with the dienyllithium species generated from **13** gave the desired adduct, which was exposed to PPTS/MeOH to produce cyclohexadienyl diol **15** as a 3:1 mixture of anti (Felkin−Ahn) and syn allylic alcohol epimers.[17]

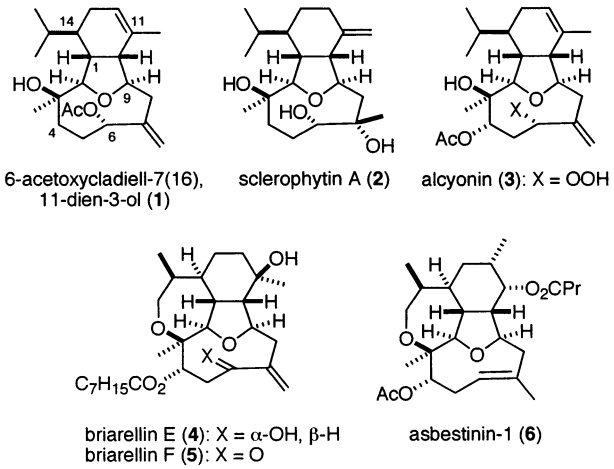
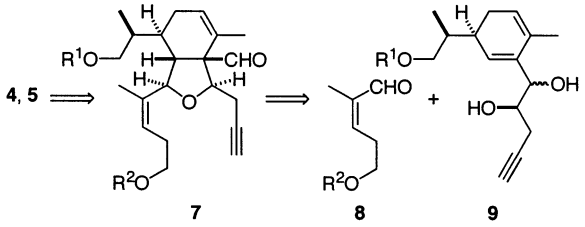


Figure 1. Representative cladiellin, briarellin, and asbestinin diterpenes.

Scheme 1



We next directed our efforts toward assembly of the oxepane-containing dioxatricyclic moiety of briarellins E (**4**) and F (**5**). Condensation of **15** and (*Z*)-α,*β*-unsaturated aldehyde **16**[18] at low temperature in the presence of *p*-TsOH/$MgSO_4$ gave the corresponding acetal,[19] which was exposed to 0.1 equiv of $SnCl_4$ to give formyl tetrahydroisobenzofuran **17** as a single stereoisomer in 84% yield for the two steps (Scheme 3). Stereospecific photolytic deformylation of **17**,[20] followed by selective cleavage of the TBDPS and TMS protecting groups with aqueous KOH provided homoallylic alcohol **18**.[21] This intermediate was stereoselectively epoxidized using (*t*-BuO)$_3$Al/*t*-BuO_2H[22,23] and the product was acetylated to afford epoxy ester **19**. Acetate-assisted opening of the epoxide of **19**,[24] followed by in situ hydrolysis and acetylation delivered diacetoxy alcohol **20** as a single isomer in good yield. Stereoselective epoxidation of **20**[25] with *m*-CPBA, followed by removal of the TIPS protecting group and triflation (Tf_2O/2,6-lutidine) of the resulting primary alcohol triggered cyclization to provide tricyclic epoxide **21**.

The conversion of intermediate **21** to briarellins E (**4**) and F (**5**) is summarized in Scheme 4. Regio- and stereoselective hydration

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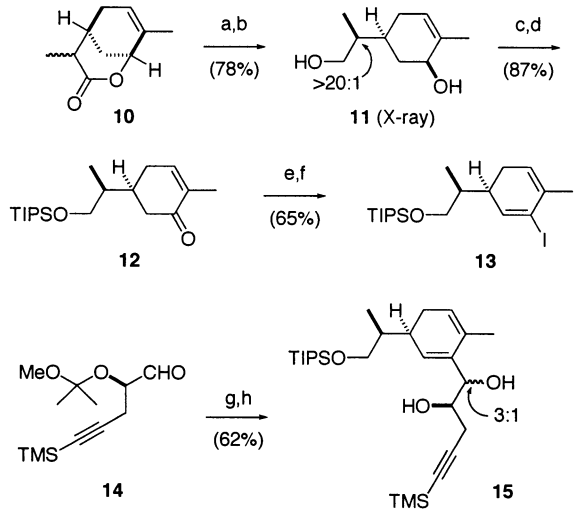
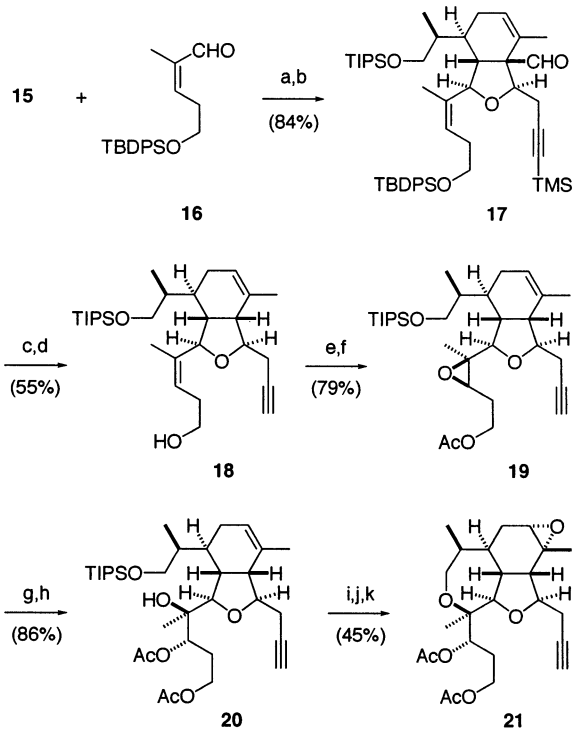
Scheme 2 [a]



[a] (a) LDA, THF, −78 °C; TMSCl, −78 °C → rt; AcOH, 0 °C → rt. (b) $LiAlH_4$, THF, −78 → 0 °C; recrystallization (78%, 2 steps). (c) TIPSCl, imidazole, DMF, rt. (d) PCC, NaOAc, CH_2Cl_2, rt (87%, 2 steps). (e) LDA, THF, −78 °C; 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, −78 °C → rt (86%). (f) $(Ph_3P)_4Pd$, LiCl, $(Me_3Sn)_2$, THF, reflux; NIS, 0 °C (76%). (g) **13**, *t*-BuLi, THF, −78 °C → rt. (h) PPTS, MeOH, rt (62%, 2 steps).

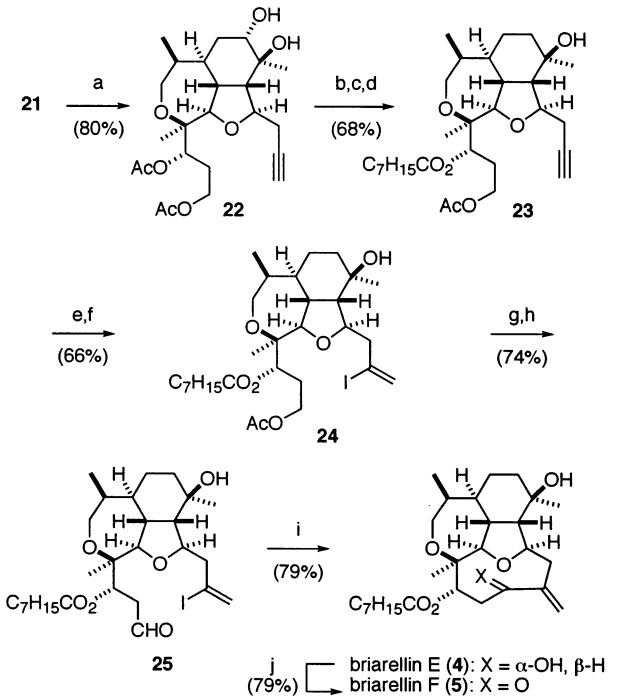
Scheme 3 [a]



[a] (a) *p*-TsOH·H_2O, $MgSO_4$, CH_2Cl_2, −78 → −20 °C. (b) 0.1 equiv $SnCl_4$, CH_2Cl_2, −78 °C → rt (84%, 2 steps). (c) *hν*, 1,4-dioxane, rt. (d) aq KOH, THF, MeOH, reflux (55%, 2 steps). (e) $(t\text{-BuO})_3Al$, $t\text{-BuO}_2H$, powdered 4 Å molecular sieves, PhMe, −20 °C (79%). (f) Ac_2O, DMAP, pyridine, rt (quant.). (g) TFA, PhMe, 0 °C → rt; H_2O. (h) Ac_2O, DMAP, pyridine, rt (86%, 2 steps). (i) *m*-CPBA, $KHCO_3$, CH_2Cl_2, 0 °C (77%). (j) *n*-Bu_4NF, THF, 0 °C (85%). (k) Tf_2O, 2,6-lutidine, $CHCl_3$, 0 °C → rt (55−68%).

of the epoxide of **21** with dilute H_2SO_4 gave diol **22**. Mesylation of the secondary alcohol of **22**, followed by treatment with $LiAlH_4$ reductively cleaved the secondary mesylate[26] and removed the two acetate groups. Selective acetylation of the primary alcohol of the resulting triol using isopropenyl acetate/$Bu_8Sn_4Cl_4O_2$,[27] followed by appendage of the octanoyl side chain produced **23**. The

Scheme 4 [a]



[a] (a) H_2SO_4, H_2O, THF, rt (80%). (b) MsCl, Et_3N, THF, rt; $LiAlH_4$ (89%). (c) $Bu_8Sn_4Cl_4O_2$, isopropenyl acetate, 50 °C (95%). (d) $C_7H_{15}COCl$, pyridine, rt (80%). (e) $Bu_3SnAlEt_2$, CuCN, THF, −30 °C (78% after 1 recycle). (f) I_2, CH_2Cl_2, rt (84%). (g) $(t\text{-Bu})_2(OH)ClSn$, MeOH, rt (93%). (h) Dess−Martin periodinane, CH_2Cl_2, rt (80%). (i) $CrCl_2$−$NiCl_2$ (100:1), DMSO−Me_2S (100:1), rt (79%). (j) Dess−Martin periodinane, CH_2Cl_2, rt (79%).

2-propynyl side chain of **23** was elaborated to a 2-iodo-2-propenyl fragment by regioselective stannylalumination-protonolysis with $Bu_3SnAlEt_2$/CuCN[28] and subsequent iododestannylation to provide vinyl iodide **24**. Selective removal of the acetate protecting group of **24** with $(t\text{-Bu})_2(OH)ClSn$/MeOH[29] followed by oxidation of the resulting primary alcohol with Dess−Martin periodinane[30] gave vinyl iodide aldehyde **25**. Nozaki−Hiyama−Kishi cyclization[8] of **25** then provided briarellin E (**4**) in 79% yield as a single stereoisomer; oxidation of **4** yielded briarellin F (**5**). Synthetic **4** was identical in all respects with a natural sample; spectral and optical rotation data for **5** compared well with those reported for the natural isolate.[6b]

In conclusion, the first total syntheses of briarellin diterpenes has been accomplished. Briarellins E (**4**) and F (**5**) were prepared in 28 and 29 steps (longest linear sequence), respectively, and 0.7% overall yield from lactone **10**.[9] These enantioselective total syntheses verify the structure assignments[6] and establish the absolute configurations for these complex oxacyclic diterpenes. These total syntheses further illustrate the power of pinacol-terminated Prins cyclizations for assembling complex polycyclic ethers.

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Supporting Information Available: Experimental procedures for key steps (preparation of **11**, **17**, **20**, **24**, and **4**); tabulated characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds **10**−**13** and **15**−**25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48 and earlier reviews in this series.
(2) For reviews, see: (a) Sung, P.-J.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705−1715. (b) Cóbar, O. M. *Rev. Latinoam. Quim.* **2000**, *28*, 46−54. (c) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556. (d) Rodríguez, A. *Tetrahedron* **1995**, *51*, 4571−4618. (e) Coll, J. C. *Chem. Rev.* **1992**, *92*, 613−631. (f) Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1992; Vol. 60, pp 1−141.
(3) The only exceptions are the pachyclavulariaenones, see: (a) Wang, G.-H.; Sheu, J.-H.; Duh, C.-Y.; Chiang, M. Y. *J. Nat. Prod.* **2002**, *65*, 1475−1478. (b) Wang, G.-H.; Sheu, J.-H.; Chiang, M. Y.; Lee, T.-J. *Tetrahedron Lett.* **2001**, *42*, 2333−2336. (c) Sheu, J.-H.; Wang, G.-H.; Sung, P.-J.; Duh, C.-Y.; Chiang, M. Y. *Tetrahedron* **2001**, *57*, 7639−7648.
(4) (a) Maia, L. F.; de A. Epifanio, R.; Eve, T.; Fenical, W. *J. Nat. Prod.* **1999**, *62*, 1322−1324. (b) Harvell, C. D.; West, J. M.; Griggs, C. *Invertebr. Reprod. Dev.* **1996**, *30*, 239−247. (c) Harvell, C. D.; Fenical, W.; Roussis, V.; Ruesink, J. L.; Griggs, C. C.; Greene, C. H. *Mar. Ecol. Prog. Ser.* **1993**, *93*, 165−173.
(5) Ospina, C. A.; Rodríguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357−363.
(6) (a) Rodríguez, A. D.; Cóbar, O. M. *Tetrahedron* **1995**, *51*, 6869−6880. (b) Rodríguez, A. D.; Cóbar, O. M. *Chem. Pharm. Bull.* **1995**, *43*, 1853−1858.
(7) Acetoxycladiell-7(16),11-dien-3-ol (**1**) and cladiell-11-ene-3,6,7-triol: (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. (b) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044. Sclerophytin A (**2**): (c) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683−2686. (d) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135−137 and ref 7b. Alcyonin (**3**): (e) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543−1546.
(8) For a recent review, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.
(9) Bicyclic lactone **10** was prepared in two steps from (*S*)-(+)-carvone: (a) 2.2 equiv 9-BBN-H, THF, 0 °C → rt; NaOH, H_2O_2, rt → reflux (73%). (b) 2,2,6,6-Tetramethyl-1-piperidinyloxy, NCS, *n*-Bu_4NCl, 2:1:1 $CHCl_3$−0.5 M aq $NaHCO_3$−0.05 M aq K_2CO_3, rt (79%).
(10) The antipode of **10** was prepared previously in four steps from (*R*)-(+)-limonene: Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 641−643.
(11) The relative configuration of **11** was corroborated by single-crystal X-ray analysis.
(12) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603−4614.
(13) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.
(14) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.
(15) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, D.-S.; Faron, F. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279.
(16) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133-2136.
(17) The configuration of the major epimer of **15** is assigned by analogy to a similar coupling in our synthesis of cladiellins, see ref 7b.
(18) (*Z*)-α,β-Unsaturated aldehyde **16** was prepared in two steps from 3-(*tert*-butyldiphenylsiloxy)propanal: (a) $Ph_3P(Et)I$, *n*-BuLi, THF, rt; I_2, −78 → −20 °C; $(TMS)_2NNa$; 3-(*tert*-butyldiphenylsiloxy)propanal, −20 °C → rt (41%). (b) *t*-BuLi, THF, −78 °C; DMF (93%).
(19) This acetal was an inconsequential mixture of four diastereomers.
(20) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906−4921.
(21) The tetrasubstituted alkene regioisomer (∼10%) formed in the deformylation step was removed by chromatography on silica gel.
(22) Takai, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3791−3795.
(23) The minor epoxide stereoisomer (∼10%) was removed by chromatography on silica gel.
(24) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, 4659−4666.
(25) (a) To avoid interaction with the five-carbon side chain, the 1-methyl-2-siloxyethyl substituent adopts a pseudoaxial orientation that shields the convex face of the hexahydroisobenzofuran. (b) The minor epoxide stereoisomer (∼10% yield) was removed by chromatography on silica gel and fully characterized (see the Supporting Information).
(26) The β C11,C12 epoxide is an observable intermediate in this sequence.
(27) Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899−2910.
(28) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064−5073.
(29) Orita, A.; Hamada, Y.; Nakano, T.; Toyoshima, S.; Otera, J. *Chem.—Eur. J.* **2001**, *7*, 3321−3327.
(30) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

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