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Total Syntheses of Anominine and Tubingensin A

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Supporting Information

ABSTRACT: A divergent strategy for the total syntheses of the indole terpenoid anominine (**1**) and its natural congener tubingensin A (**2**) has been developed. The common intermediate **11** bearing all of the required stereogenic centers for both natural products was first assembled by employing a Ueno−Stork radical cyclization and a $Sc(OTf)_3$-mediated Mukaiyama aldol reaction to form the key C−C bonds in a stereocontrolled manner. The route to anominine features a radical deoxygenation followed by an efficient side-chain installation, while the path to tubingensin A exploits a CuOTf-promoted 6π-electrocyclization/aromatization sequence to forge the central region of the pentacyclic scaffold.

Anominine (**1**) is a structurally representative member of a growing family of naturally occurring indole diterpenoids that also includes tubingensin A (**2**), aspernomine (**3**), aflavinine (**4**), and 10,23-dihydro-24,25-dehydroaflavinine (**5**) (Scheme 1), which were initially isolated from *Aspergillus* spp. by Gloer and co-workers.[1] Several other members of this family [e.g., 17-hydroxyeujindole (**6**) (Scheme 1)] were recently isolated from *Eupenicillium javanicum*.[2] Not surprisingly, these intricate molecular architectures were found to possess interesting biological properties, such as antiinsectant, antiviral, and anticancer activities.[1] Notably, the only total synthesis of anominine to date was accomplished elegantly by Bonjoch and co-workers in 2010, while the syntheses of its congers remain a challenge.[3]

On the basis of the intriguing structural relationships among them, we postulated a biosynthetic network connecting the above-mentioned molecules to the parent natural product **1**, as shown in Scheme 1. On one hand, benzylic oxidation of **1** could generate cationic species **7**, which may then enter two different paths: (a) elimination to form triene **8** followed by a 6π-electrocyclization/aromatization sequence to give **2** or (b) cationic olefin cyclization and oxidation state adjustment to afford **5**. Furthermore, the terminal C=C bond of **5** may migrate to afford its isomer **4**, while a Friedel−Crafts cyclization occurring at the indole C4 position of **5** would render **6**. On the other hand, oxidative dearomatization of the indole moiety of **1** could generate a reactive intermediate **9**, which may undergo an iminium−olefin cyclization to give tertiary carbenium ion **10** followed by a Friedel−Crafts/fragmentation sequence to furnish **3**.[4] Additionally, simple dehydration and aromatization of **10** may provide another path toward **2**. Despite the lack of biochemical evidence to support it, we launched a total synthesis program aimed at exploring the biosynthetic speculation outlined in Scheme 1.

Inspired by the above hypothesis, we undertook a retrosynthetic analysis involving a common intermediate as the junction of the two approaches toward **1** and **2**, as shown in Scheme 2. To avoid the uncertainty in direct benzylic oxidation of a sensitive indole derivative (Scheme 1), alcohol **11** was considered as a practical and versatile intermediate. First, it could serve as a convenient precursor for triene **12**, the substrate for the 6π-electrocyclization/aromatization reaction proposed in Scheme 1. Second, it should readily undergo radical or cationic deoxygenation to generate the desired oxidation level for anominine. In addition, its lactol motif could be used as a convenient handle to install the olefinic side chains for both **1** and **2**. Straightforward disassembly of **11** through Grignard addition and Wittig processes would result in hydroxyketone **13**, which could be further traced back to tricyclic ketone **14**. In a forward manner, **13** was expected to be available through an aldol reaction of **14** and formaldehyde. We considered the next disconnection at the C20−C21 bond (anominine numbering system) of **14**; obviously, efficient introduction of the all-carbon quaternary center at C20 was one of the most challenging bond constructions in our plan because of both steric and stereochemical issues. Thus, a Ueno−Stork radical cyclization employing the corresponding iodoacetal as the substrate was envisioned to solve the above problem. This iodide could be readily assembled from known hydroxyenone **15** bearing the three stereogenic centers desired for both natural products.

On the basis of the above analysis, we first investigated the synthesis of the basic building block **14** (Scheme 3). To ensure our material supply, the preparation of **15**[5] was streamlined by taking advantage of a scalable and selective Mukaiyama−Michael addition process.[6] Starting with readily available and optically active ketone **16**,[7] regioselective trimethylsilyl (TMS) enol ether formation followed by $BF_3{\cdot}OEt_2$-promoted diastereoselective 1,4-addition and subsequent Robinson annulation afforded bicyclic enone **17** in 47% overall yield.[6] Compound **17** was then converted into **15** in two steps.[5b] With **15** in hand, we focused our attention on the formation of the C20−C21 bond.

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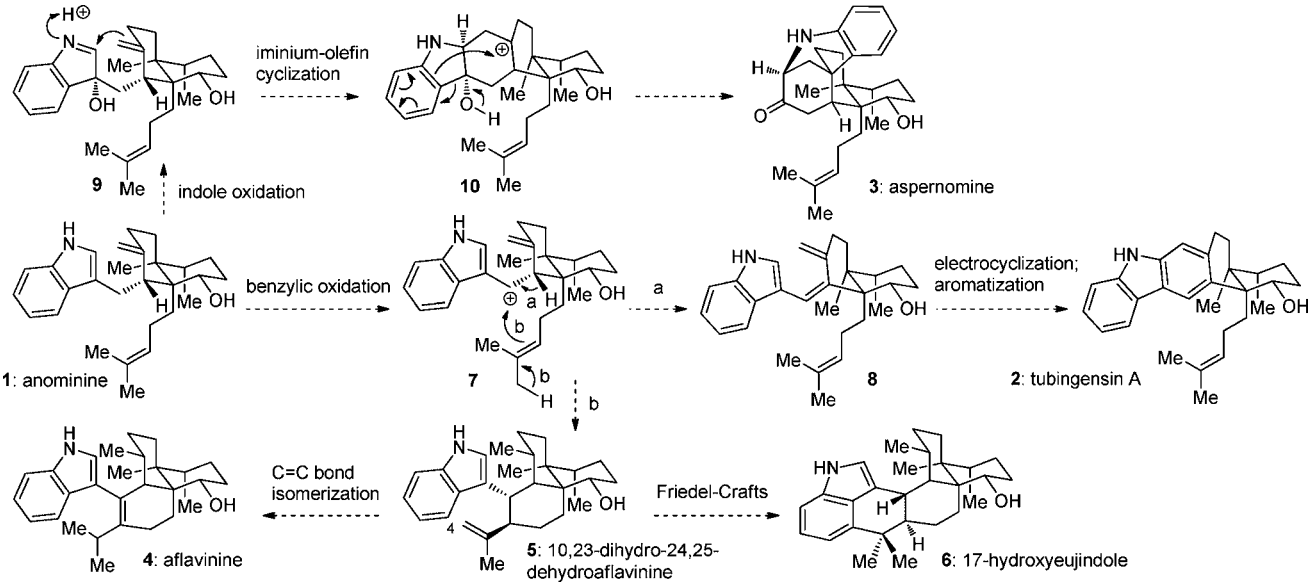
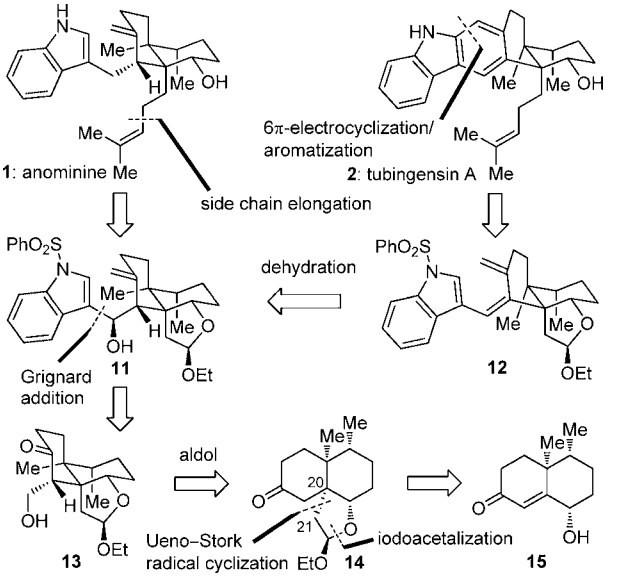
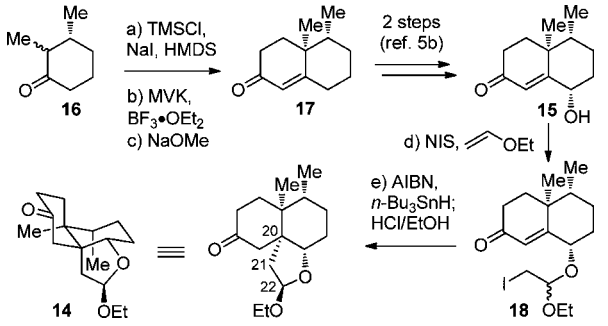
Scheme 1. Postulated Biosynthetic Relationship among Some Members of the Anominine Family



Scheme 2. Retrosynthetic Analysis for Anominine (1) and Tubingensin A (2)



Scheme 3. Construction of Tricyclic Ketone 14



[a]Reagents and conditions: (a) TMSCl (3.0 equiv), HMDS (4.0 equiv), NaI (4.0 equiv), MeCN, 0 → 22 °C, 2 h; (b) MVK (3.0 equiv), $BF_3{\cdot}OEt_2$ (0.2 equiv), MeOH (1.0 equiv), CH_3NO_2, −20 °C, 1 h; (c) NaOMe (1.5 equiv, 1.0 M in MeOH), 45 °C, 5 h, 47% (three steps); (d) NIS (6.0 equiv), ethyl vinyl ether (8.0 equiv), CH_2Cl_2, −20 °C, 40 min, 98% (ca. 1:1 mixture of diastereomers); (e) AIBN (0.5 equiv), *n*-Bu_3SnH (2.0 equiv), toluene, 80 °C, 2 h, then ethanolic HCl (5.0 equiv, 2.0 M), CH_2Cl_2, 0 → 22 °C, 1 h, 65%.

Iodoetherification of **15** in the presence of ethyl vinyl ether and *N*-iodosuccinimide (NIS) gave **18** as a ca. 1:1 mixture of diastereomers in 98% yield, setting the stage for the planned radical cyclization.[8] After examination of a variety of conditions (initiator, temperature, addition protocol) for this transformation, we were pleased to find that the cyclization proceeded smoothly upon slow addition of azobis(isobutyronitrile) (AIBN) and *n*-Bu_3SnH at 80 °C to afford a mixture of tricyclic ketone **14** and its C22 epimer; treatment with ethanolic HCl gave a single diastereomer. Thus, **14** was obtained in 65% overall yield from **18**. The above protocol was also applied to the bromo counterpart of **18** and proved to be equally effective; however, the preparation of the bromoacetal under standard conditions was much less efficient. Notably, our parallel investigation of intermolecular 1,4-addition (or its equivalent reaction) to **15** or its hydroxyl-protected forms turned out to be disappointing. For example, cuprate-mediated conjugate addition and Sakurai reaction were both fruitless, while treatment with a more powerful reagent such as Et_2AlCN only gave 1,4-adducts in low yield and poor diastereocontrol. In an alternative attempt, the 1,2-adduct of allyl-MgBr to **15** was subjected to anionic oxy-Cope conditions but remained inert at elevated temperature.

With **14** in hand, our next challenge was to install the indole-containing side chain and construct key intermediate **11** (Scheme 4). To our delight, selective C11 deprotonation with lithium hexamethyldisilazide (LiHMDS) at −78 °C followed by trapping of the resulting enolate with TMSCl afforded the corresponding silyl enol ether, which reacted with formaldehyde under $Sc(OTf)_3$-mediated aqueous Mukaiyama aldol conditions[9] to furnish hydroxyl ketone **13** with good overall efficiency. Notably, indole-3-carboxaldehyde or its *N*-protected versions proved to be unreactive under these Lewis acidic or other basic aldol conditions. Through a sequence of silylation, Wittig methylenation, desilylation, and oxidation with Dess–Martin periodinane (DMP), alcohol **13** was readily converted

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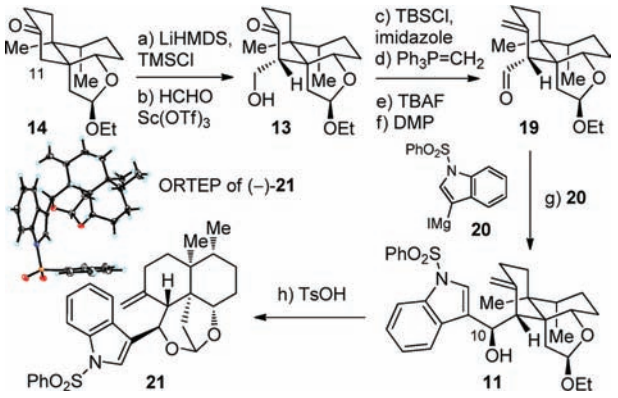
Scheme 4. Assembly of Key Intermediate 11

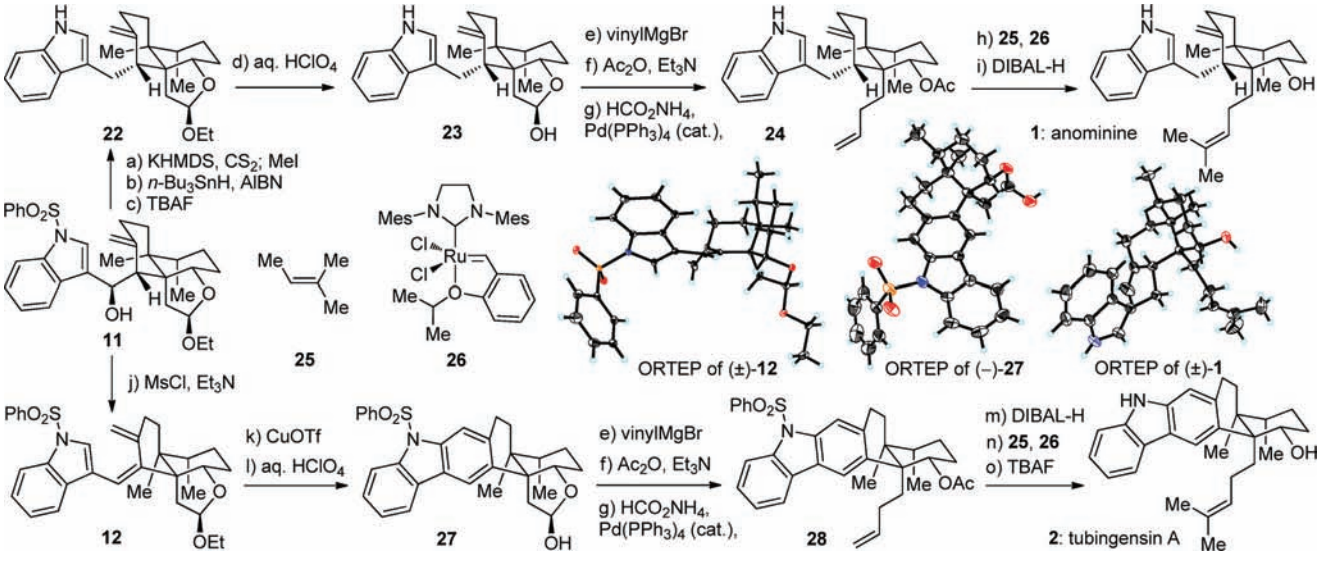


[a]Reagents and conditions: (a) TMSCl (2.0 equiv), LiHMDS (3.0 equiv, 1.0 M in THF), THF, −78 °C, 40 min; (b) $Sc(OTf)_3$ (0.2 equiv), 37 wt % aq. formalin (10.0 equiv), THF, 22 °C, 40 min, 76% (two steps); (c) TBSCl (2.0 equiv), imidazole (4.0 equiv), DMF, 22 °C, 1 h; (d) *n*-BuLi (2.0 equiv), $Ph_3P^+CH_3I^-$ (2.2 equiv), THF, −78 → 0 °C, 30 min, then 0 °C, 30 min; (e) TBAF (2.0 equiv), THF, 22 °C, 1 h, 76% (three steps); (f) DMP (1.5 equiv), CH_2Cl_2, 0 → 22 °C, 1 h, 84%; (g) **20** (5.0 equiv), THF, −78 °C, then 22 °C, 40 min, **11**: 88%, C10 epimer of **11**: 10%; (h) $TsOH·H_2O$ (0.1 equiv), CH_2Cl_2, 22 °C, 1 h, 99%.

to aldehyde **19** in good overall yield. Treatment of the latter with Grignard reagent **20** provided our subtarget, alcohol **11**, together with its C10 epimer as a minor product. Interestingly, **11** underwent rapid cyclization to give polycyclic acetal **21** under acidic conditions (e.g., TsOH or HCl generated from old chloroform). The structure of **21** (mp 184−187 °C, 1:1 EtOAc/petroleum ether), which was determined by X-ray crystallographic analysis, indirectly confirmed the stereochemical assignment of alcohol **11**.

Having forged all of the requisite stereochemical information into **11**, we focused our attention on completion of the anominine synthesis (Scheme 5). Thus, xanthate formation and radical deoxygenation followed by desulfonylation with tetrabutylammonium fluoride (TBAF) furnished **22** with good overall efficiency,[10] and **22** was smoothly converted to lactol **23** by acidic hydrolysis. Surprisingly, **23** proved to be highly resistant to nucleophilic attack. Under standard conditions, a variety of Grignard, lithium, and Wittig reagents as well as hydride sources were examined for the lactol-opening reaction with little success, and only $LiAlH_4$ slowly reduced **23** to the corresponding diol at ambient temperature. The unusual stability of **23** could presumably be attributed to the equilibrium between this lactol and its ring-opened aldehyde form being heavily biased to the former side because of the crowded nature of the latter. We suspected that a different solvent might have a subtle influence on this equilibrium, and, indeed, treatment of **23** with vinyl-MgBr in toluene at 60 °C for 5 h afforded the desired ring-opening addition product, albeit with incomplete conversion. The diol product was taken directly into a sequence of bisacetylation (Ac_2O/Et_3N) and Tsuji reduction[11] [$Pd(PPh_3)_4$ (cat.), HCO_2NH_4] to furnish the monodeoxygenated product **24** with acceptable overall efficiency. Finally, cross-metathesis between **24** and freshly distilled 2-methyl-2-butene (**25**) promoted by Hoveyda−Grubbs II catalyst (**26**)[3a] and subsequent cleavage of the acetyl group with diisobutylaluminum hydride (DIBAL-H) afforded anominine (**1**) in 83% yield over the two steps. The physical properties, including the optical rotation of synthetic **1**, matched those reported for the natural material,[1a] which was also consistent with the assignment of the absolute

Scheme 5. Divergent Approaches toward Anominine and Tubingensin A



[a]Reagents and conditions: (a) KHMDS (5.0 equiv, 0.5 M in toluene), CS_2 (5.0 equiv), THF, −78 °C, 1 h, then MeI (5.0 equiv), −78 → 22 °C, 1 h; (b) *n*-Bu_3SnH (2.0 equiv), AIBN (0.5 equiv), toluene, 110 °C, 1 h, 72% (two steps); (c) TBAF (3.0 equiv, 1.0 M in THF), toluene, 110 °C, 2 h, 86%; (d) aq. $HClO_4$ (1.0 M)/THF (1:1), 22 °C, 8 h, 76%; (e) vinyl-MgBr (10.0 equiv, 0.7 M in THF), toluene, 0 °C, then 60 °C, 5 h; (f) Ac_2O (10.0 equiv), Et_3N (20 equiv), DMAP (1.0 equiv), CH_2Cl_2, 0 °C, then 40 °C, 5 h; (g) $Pd(PPh_3)_4$ (0.3 equiv), HCO_2NH_4 (10.0 equiv), toluene, 80 °C, 40 min, 54% for **24**, 52% for **28** (three steps); (h) **26** (0.2 equiv), **25**, 22 °C, 24 h; (i) DIBAL-H (5.0 equiv, 1.0 M in hexanes), CH_2Cl_2, −78 °C, 30 min, 83% (two steps); (j) MsCl (5.0 equiv), Et_3N (10.0 equiv), CH_2Cl_2, −78 → 22 °C, 5 h, 79%; (k) $(CuOTf)_2$·toluene (1.0 equiv), CH_3CN, 22 °C, 4 h; (l) aq. $HClO_4$ (4.0 M)/THF (1:1), 22 °C, 4 h, 70% (two steps); (m) DIBAL-H (5.0 equiv, 1.0 M in hexanes), CH_2Cl_2, −78 °C, 30 min, 87%; (n) **26** (0.2 equiv), **25**, 22 °C, 24 h; (o) TBAF (5.0 equiv, 1.0 M in THF), toluene, 110 °C, 2 h, 78% (two steps).

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configuration of **1** by Bonjoch.[3a] Further confirmation of the structure of **1** came from X-ray crystallographic analysis of single crystals of (±)-**1** (mp 178−180 °C, 1:1 EtOAc/petroleum ether).[12]

Encouraged by the successful assembly of **1**, we continued to investigate the synthesis of our second target, tubingensin A (**2**), from intermediate **11** via the envisioned 6π-electrocyclization/aromatization strategy (Scheme 5). Dehydration of **11** in the presence of mesyl chloride (MsCl) and Et_3N gave triene **12** as a single geometric isomer in 79% yield,[10] the structure of which was determined by X-ray crystallographic analysis.[12] Triene **12** was stable at ambient temperature with no detectable electrocyclization or double-bond isomerization. However, conventional thermal conditions failed to initiate the desired electrocyclization of **12** but resulted in its decomposition. Fortunately, CuOTf was found to be a very efficient promoter of the 6π-electrocyclization on our substrate, and the aromatization reaction spontaneously occurred in one pot to furnish the desired pentacyclic carbazole scaffold.[13] Subsequent acetal hydrolysis (aq. $HClO_4$) afforded lactol **27** in 70% overall yield. The structure of **27** (mp 182−183 °C, 1;1 EtOAc/petroleum ether) was confirmed by X-ray crystallographic analysis (see the ORTEP in Scheme 5). With **27** in hand, we carried out the same side-chain elongation protocols as in the synthesis of **1** to reach tubingensin A (**2**) via intermediate **28** (Scheme 5). The physical properties of our synthetic sample were identical to those reported for the natural product.[1b] The consistency of the sign and magnitude of the optical rotation of the two samples also assigned the absolute configuration of the naturally occurring **2**.

In conclusion, we have described efficient total syntheses of anominine and tubingensin A, the latter of which has been accomplished for the first time. A divergent strategy based on a versatile common intermediate **11** was successfully applied in our syntheses. A series of reactivity and selectivity problems were encountered and overcome on the journey. These studies are expected to facilitate the systematic synthetic and biological investigations of the members of this indole terpenoid family. These ongoing studies should further corroborate the biosynthetic speculations on this family of natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gloer, J. B.; Rinderknecht, B. L.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 2530. (b) TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1989**, *54*, 4743. (c) Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343 and references cited therein.

(2) (a) Nakadate, S.; Nozawa, K.; Horie, H.; Fujii, Y.; Yaguchi, T. *Heterocycles* **2011**, *83*, 351. (b) Nakadate, S.; Nozawa, K.; Yaguchi, T. *Heterocycles* **2011**, *83*, 1867.

(3) (a) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966. (b) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *Org. Biomol. Chem.* **2008**, *6*, 772. (c) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, 337.

(4) Liu, Y.; McWhorter, W. W., Jr.; Hadden, C. E. *Org. Lett.* **2003**, *5*, 333.

(5) (a) Paquette, L. A.; Wang, T.-Z.; Philippo, C. M. C.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367. (b) Díaz, S.; González, A.; Bradshaw, B.; Cuesta, J.; Bonjoch, J. *J. Org. Chem.* **2005**, *70*, 3749.

(6) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387.

(7) Dagneau, P.; Canonne, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2817.

(8) For a comprehensive review of Ueno−Stork radical cyclization, see: Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, 1903.

(9) Kobayashi, S. *Synlett* **1994**, 689, and references therein.

(10) The C10 epimer of **11** was converted to compounds **22** and **12**, respectively, in a similar manner and with essentially the same overall efficiency.

(11) Tsuji, J.; Nisar, M.; Shimiiu, I. *J. Org. Chem.* **1985**, *50*, 3416.

(12) Compounds **1** and **12** were prepared in both optically active and racemic forms; only the racemic compounds were obtained as high-quality single crystals suitable for X-ray crystallographic analysis.

(13) Abe, T.; Ikeda, T.; Yanada, R.; Ishikura, M. *Org. Lett.* **2011**, *13*, 3356.