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A concise synthesis of the cortistatin core

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Abstract

We describe a concise and convergent route to the core matrix of the cortistatin steroidal alkaloids. The salient features of the synthesis are the Snieckus cascade methodology and the Masamune alkylative dearomatization. This chemistry lends itself to a total synthesis of the cortistatins and to the development of a SAR program based on diverted total synthesis.

In 2006, Kobayashi and coworkers reported the isolation of a novel class of steroidal alkaloids, the cortistatins, from the marine sponge, *Corticium simplex*.[1] Among them, cortistatin A, in particular, exhibited cytostatic antiproliferative activity against human umbilical vein endothelial cells (HUVECs) at concentrations as low as 100 pM. The high selectivity observed for the endothelial (HUVEC) cell line, in comparison with other normal and cancerous cell lines, suggests that cortistatin A (**1**) could, in principle, be a selective angiogenesis inhibitor.[2] Inspired by the potent biological activity and unusual structural elements of the cortistatins, a number of groups have been engaged in total synthetic efforts directed at this challenging family of natural products.[3] The recent success of Baran and coworkers in converting prednisone to cortistatin A (**1**) is a milestone in this field.[4] Even more recently, a total synthesis of cortistatin A (**1**) was accomplished by Nicolaou and coworkers.[5]

Our own initial approach to the synthesis of cortistatin A[6] focused on the preparation of a key pentacyclic intermediate, cf. **8**. This advanced compound would hopefully serve as a precursor to the natural product itself. Even more importantly, it would provide a useful synthetic platform from which to gain entry to a range of cortistatin analogs through diverted total synthesis.[7] Unexpected problems encountered in our initial synthetic route[6] led us to consider an alternative and perhaps more interesting approach to the synthesis of intermediate **8**. This modified route would culminate in a Masamune-inspired alkylative dearomatization[8] of compound **7**. As outlined in Scheme 1, we envisioned taking advantage of the elegant Snieckus cascade methodology[9] for construction of tetracyclic compound **7** from the relatively simple precursors, **2** and **3**. The progression would commence with 1,2-addition of the aryllithium derived from **2** to α,β-unsaturated aldehyde **3**, thereby generating alkoxide **4**. Subsequent intramolecular carbamate migration, followed by 1,4-elimination would give rise to quinomethide **6**. We anticipated that the latter would undergo 6π-electrocyclization to produce an intermediate of the type **7**.

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At the planning level, we could not be certain of the stereochemical outcome of the 6π-electrocyclization (at C_8). We postulated that intermediate **7** would likely be the thermodynamically favored epimer, due to the *trans/anti* stereoconnectivity of the angular methyl group (C_{18}), the hydrogen on C_{14} and the angular 2-carbon chain. Finally, intramolecular alkylation of **7** should provide access to the key pentacyclic core system (**8**) of the cortistatins.

A model study was conducted to evaluate the likelihood of the applicability of the Snieckus paradigm to our system. As shown in Scheme 2, aryl bromide **9**[10] was exposed to the action of *t*BuLi in ether for 30 min at −78 °C. Following addition of compound **10**,[11] the reaction mixture was warmed to room temperature and stirred overnight. We were pleased to find that the desired product, **14**, could be isolated, albeit at the time, in only 33% yield. Selective deprotection of the primary TBS-ether afforded compound **15**,[12] which was transformed to mesylate **16** in excellent yield. Finally, the phenoxide, presumably generated by treatment of compound **16** with anhydrous TBAF in THF at room temperature, was further heated to 130 °C to give the desired product **17** in 85% yield.

Having established the viability, at least in principle, of our general vision of the problem it was now appropriate to turn to the synthesis of aldehyde **22**. As outlined in Scheme 3, alkylation of the Hajos-Parrish mono-ketal **18** with bromide **19** afforded **20** in 58% yield.[13] Extended triflate formation,[14] followed by Pd-catalyzed carboxylation[15] of the crude triflate gave the methyl carboxylate, which was further reduced by DIBAL-H to furnish compound **21** (50% yield over three steps starting from **20**). The resultant allylic alcohol was oxidized to the desired aldehyde **22** through treatment with IBX.[16]

When aldehyde **22** was exposed to the kind of reaction conditions described above (see Scheme 2), only the 1,2-addition product was isolated, as a 1:1 mixture of diastereomers. However, when the reaction mixture was further heated overnight at 80 °C, the tetracyclic product **23** was obtained in 44% yield, though with the undesired stereochemistry at C_8, as evidenced by X-ray crystallography of the deprotected product **24** (Scheme 4).[17] However, when compound **23** was heated at 130 °C in THF, *it epimerized to the desired compound **25** in quantitative yield, presumably through a sequence comprised of retro-6π-electrocyclization and 6π-electrocyclization*. This transformation is consistent with our expectation that compound **25**, possessing a 1,3-*cis* diaxial relation between the angular methyl and the angular 2-carbon chain ($-CH_2CH_2OTBS$), is the thermodynamically favored epimer. We further envisioned that, if the reaction mixture arising from treatment of aldehyde **22** with aryllithium derived from **9** were heated at 130 °C, the desired product, **25** could be obtained. Indeed, upon heating the reaction mixture at 130 °C overnight, the hoped for product **25** was obtained in high yield (71%). Following selective deprotection and subsequent mesylation of the primary alcohol, intermediate **26** was in hand. The latter smoothly underwent the desired alkylative dearomatization to produce the pentacyclic core of the cortistatins in excellent (ca. 88%) yield. The structure of compound **27** was unambiguously confirmed by X-ray crystallography.[18]

In summary, we have devised and reduced to practice a concise and efficient route to the core matrix of the cortistatins. Critical to its success was an orchestration of carbanion chemistry, an O→O acyl transfer driven rearrangement, quinonemethide formation, and electrocyclic re-aromatization setting the stage for alklyative dearomatization (see **9**→**27**). This chemistry could well be extended to a total synthesis of the cortistatin family of steroids. Equally important, it sets the stage for realistic SAR work based on diverted total synthesis.[7]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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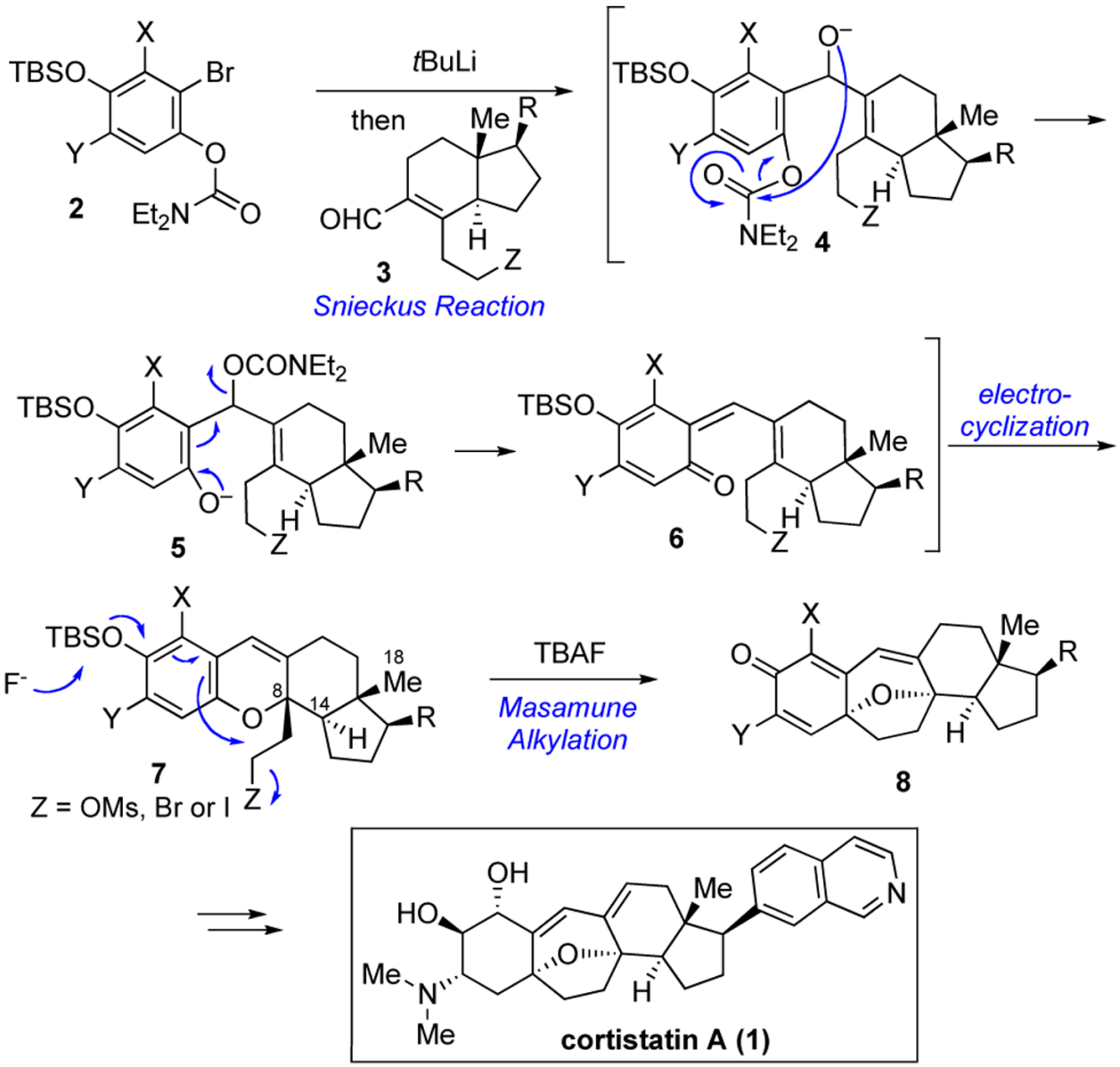
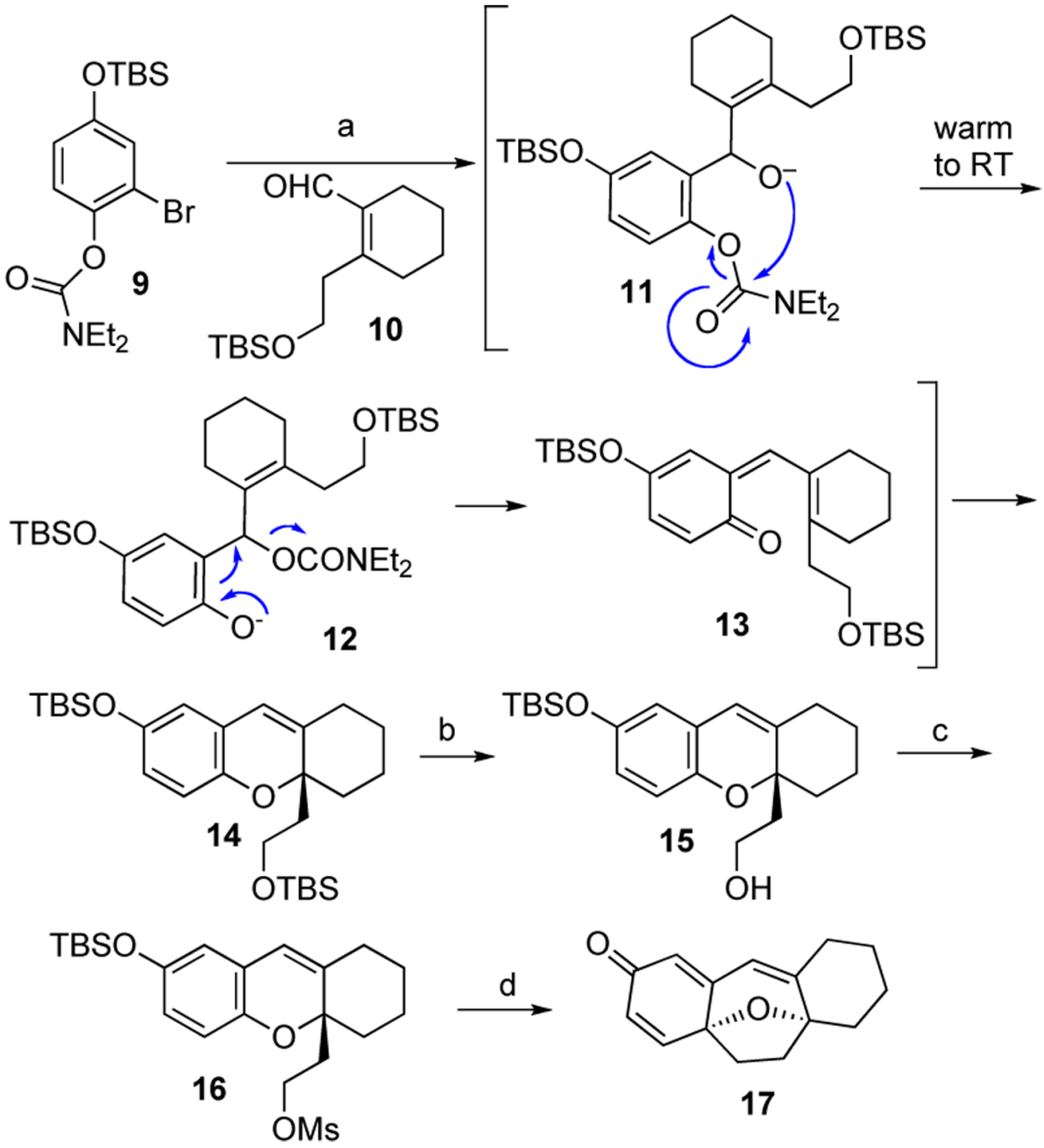
17. CCDC 696105 contains the supplementary crystallographic data for compound **24**.
18. CCDC 696762 contains the supplementary crystallographic data for compound **27**.

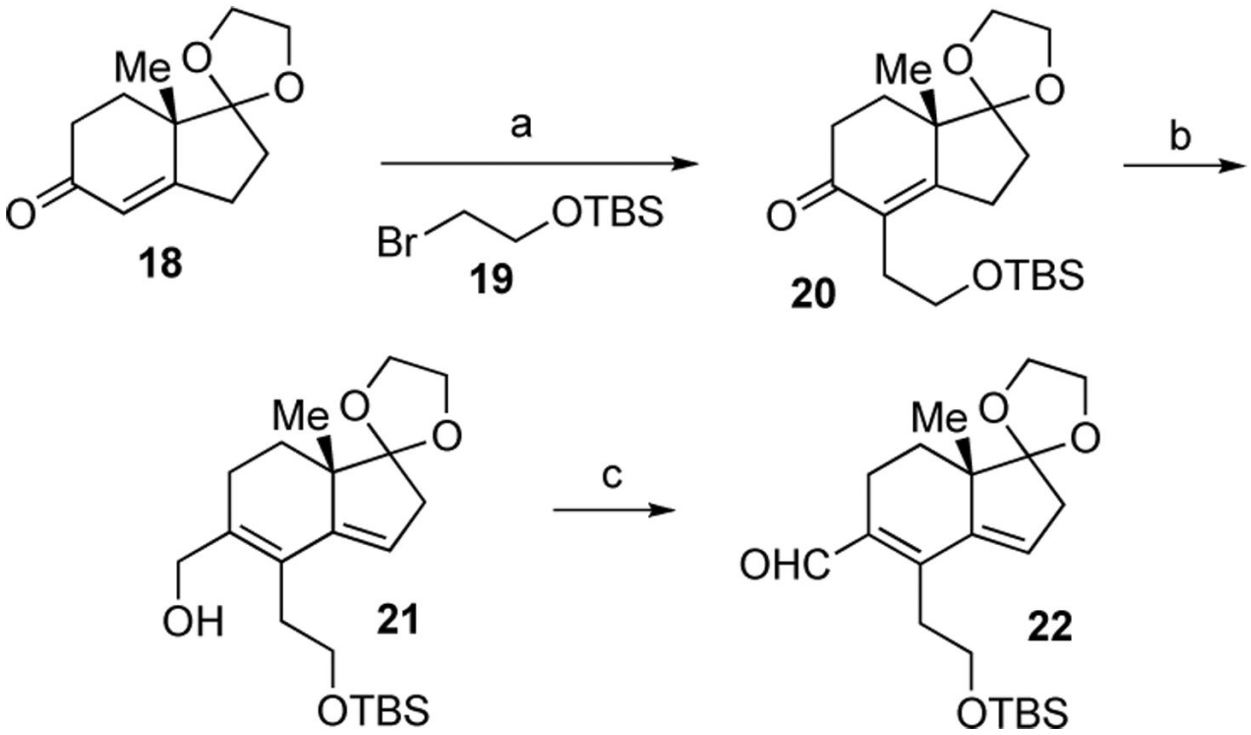


Scheme 1.
Synthetic strategy toward cortistatin A (**1**).



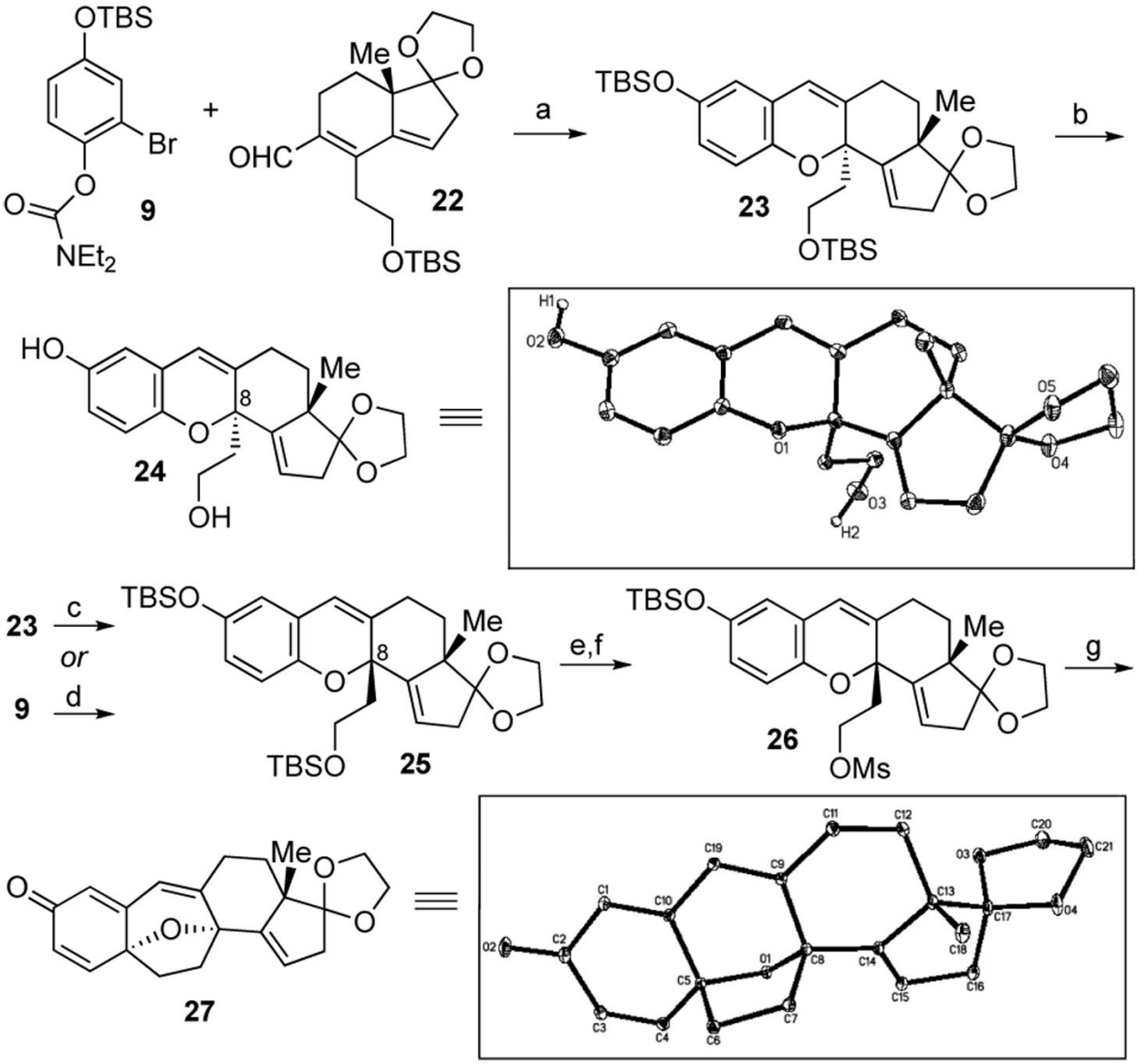
Scheme 2.

Model Study. Reagents and conditions: (a) *t*BuLi, Et_2O, −78 °C, 30 min, then **10**, then warm to RT, overnight, 33%; (b) I_2, MeOH / THF (1 / 1), RT, 3 h, 80%; (c) MsCl, pyridine, CH_2Cl_2, 0 °C → RT, 6 h, 98%; (d) TBAF, THF, RT, 5 min, then 130 °C, 20 min, 85%.



Scheme 3.

Synthesis of aldehyde **22**. Reagents and conditions. (a) NaH, DMSO; then **19**, RT, 4 h, 58%; (b) (i) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C, 30 min; (ii) $Pd(OAc)_2$, PPh_3, iPr_2NEt, CO, MeOH, 50 °C, 48 h; (iii) DIBAL-H, CH_2Cl_2, 0 °C, 30 min, 50% from **20**; (c) IBX, ethyl acetate, reflux, 7 h, 90%.



Scheme 4.

Synthesis of the pentacyclic core of cortistatin A. Reagents and conditions. (a) *t*BuLi, Et_2O, −78 °C, 30 min, then **22**, then heated to 80 °C, overnight, 44%; (b) TBAF, THF, 0 °C, 2 h, 96%; (c) THF, 130 °C, overnight, 100%; (d) *t*BuLi, Et_2O, −78 °C, 30 min, then **22**, then heated to 130 °C, overnight, 71%; (e) I_2, MeOH / THF (1 / 1), RT, 2 h, 83%; (f) MsCl, Pyridine, CH_2Cl_2, 0 °C → RT, 94%; (g) TBAF, THF, RT, 5 min, then 130 °C, 20 min, 88%.