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The Total Synthesis of Spirotenuipesines A and B

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Our laboratory seeks to develop natural product-derived lead compounds for the treatment of neurodegenerative disorders.[1] We noticed reports concerning two novel natural products, spirotenuipesines A (**1a**) and B (**1b**), isolated from the entomopathogenic fungus, *Paecilomyces tenuipes*, by Oshima and co-workers in 2004.[2] Upon introduction to 1321N1 human astrocytoma cells, these compounds appear to facilitate the expression and release of neurotrophic factors, which promote neuronal differentiation of rat pheochromocytoma cells (PC-12). We report herein the total synthesis of spirotenuipesines A and B.

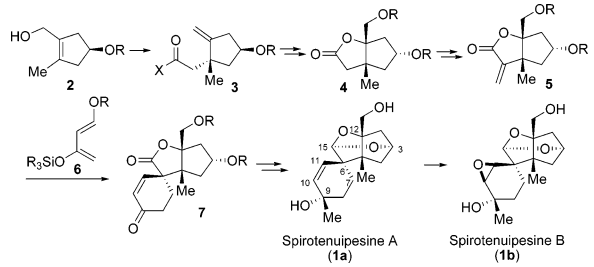
The central notion of our total synthesis approach anticipated that Diels−Alder reaction of a generic α-methylene lactonic dienophile (see **5**) with a synergistic diene (cf. **6**) would occur from the *exo*-face of the bicyclic system, giving rise, after unraveling of the primary adduct, to the enone **7**. There would subsequently be required adjustment of the functionality at C_9, reduction of the lactonic carbonyl at C_{15} to the hemiacetal oxidation level, followed by acetal formation between a concave disposed C_3 hydroxyl group and C_{15}. Without specifying in detail how these post-Diels−Alder endgame requirements would be accomplished, it seemed that means could be found. Indulging this line of reasoning further, it seemed that **4** could be reached from **3** by an again unspecified oxidative lactonization.

We had expected that **3** might arise through entry from a menu of Claisen-like rearrangements of precursor **2**. It was presumed, *with what turned out to be unwarranted optimism*, that the Claisen step would occur with high stereoselectivity, presumably *anti* to the resident protected oxygen group. There would thus be required eventual inversion of configuration at C_3 (see **2** → **3** → **4**, Scheme 1). The synthesis started with the known **8**,[3] which was advanced to **9**[4] and then to **10**, as shown in Scheme 2. It should be noted that the RCM route shown here constitutes a *major simplification* in the preparation of **10**.[5] Unfortunately, all attempts at Claisen rearrangements of **10** gave rise to 1:1 mixtures of **11** and **12**. While we could re-incorporate each component into our synthesis by reconvergence, this carried with it a clear compromising of efficiency, not to speak of an undermining of aesthetic acceptability. We attempted to evaluate, from an experimental standpoint, several possible explanations for the surprising breakdown of face selectivity. These investigations will be described in due course.

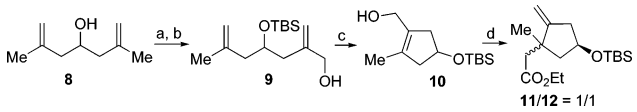
We envisioned an alternative to reach the required γ,δ-unsaturated esters. In this route, the primary alcohol of **10** was acetylated (Scheme 3). Following cleavage of the silyl group, the resultant secondary alcohol at the future C_3 was converted to its diazoacetyl derivative, **13**. Intramolecular cyclopropanation, as shown, afforded the activated cyclopropane **14**.[6]

As explained below (see Scheme 5), the stereoguidance of a Claisen-based rearrangement of a system such as **10** must depend on the characteristics of the two diastereotopic surfaces of the cyclic olefin and cannot be readily controlled by tethering. To exploit this difference, it would be necessary to affect the controlled rupture of the required Walsh bond[7] of the cyclopropane (see asterisk in **15**). Definition of the optimal way to accomplish this type of overall vicinal reductive cleavage is still a work in progress. The preferred protocol for this purpose may differ from case to case as a function

Scheme 1. Synthetic Strategy toward Spirotenuipesines A and B

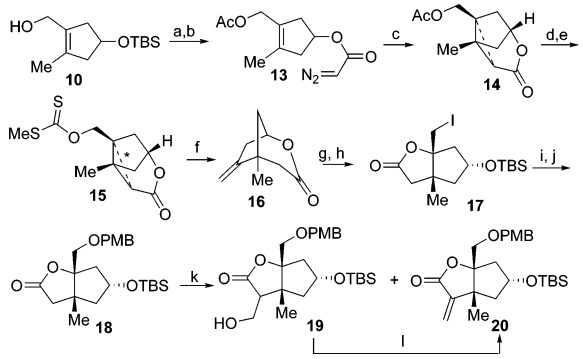


Scheme 2 [a]



[a] Key: (a) TBSCl, imidazole, DMF, rt, 95%; (b) 5% SeO_2 on silica gel, *t*-BuOOH (5−6 M in nonane), CH_2Cl_2, rt, 40−50%; (c) Grubbs second generation catalyst, benzene, reflux, 82%; (d) propionic acid, triethylorthoacetate, 180 °C, 87%, 1:1 dr.

Scheme 3 [a]



[a] Key: (a) Ac_2O, DMAP, TEA, CH_2Cl_2, rt; TBAF, THF, rt, 84% over two steps; (b) glyoxylic acid chloride tosylhydrazone, *N*,*N*-dimethylaniline; TEA, CH_2Cl_2, 0 °C to rt, 88%; (c) bis(*N*-*tert*-butylsalicylaldiminato) copper (II), toluene, reflux (slow addition of s.m.), 91%; (d) K_2CO_3, MeOH, rt; (e) KHMDS; CS_2; MeI, THF, rt; (f) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 5 h, 60% over three steps; (g) KOH, MeOH, 60 °C; HCl then $NaHCO_3$, KI, I_2, THF, rt; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 77% over three steps; (i) AIBN, Bu_3SnH, dry air, toluene, 60 °C; then $NaBH_4$, EtOH, 0 °C, 79%; (j) PMB trichloroacetimidate, CSA, CH_2Cl_2, 95%; (k) LDA, THF, −78 °C; then CH_2O (gas), 0 °C; then rt, **19**: 65%, **20**: 28%; (l) MsCl, TEA, CH_2Cl_2, 0 °C to rt; then DBU, CH_2Cl_2, rt, 95%.

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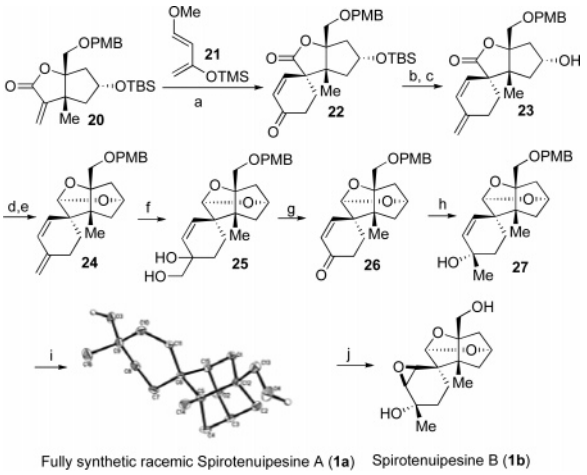
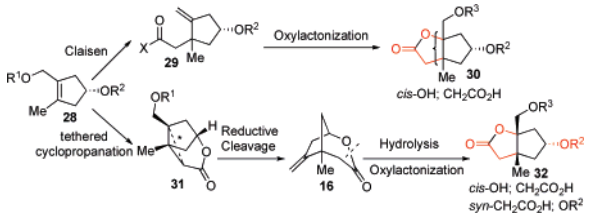
Scheme 4 [a]



[a] Key: (a) **21**, methylene blue, toluene, 180 °C; then amberlite I-120 (acidic), CH_2Cl_2, rt, 90%, 8:1 dr; (b) $Ph_3P^+CH_3I^-$, KHMDS, −78 °C; then rt, 96%; (c) TBAF, THF, rt, 97%; (d) DIBAL-H, CH_2Cl_2, −78 °C, 20 min; (e) CSA, 4 Å MS, CH_2Cl_2, rt, 90% over two steps; (f) OsO_4, pyridine, rt; (g) $NaIO_4$, THF/H_2O (1:1), 0 °C to rt, 2 h, 90% over two steps; (h) MeLi, $CeCl_3$, THF, −78 °C, then 0 °C, 95%, 6:1 dr; (i) DDQ, CH_2Cl_2/buffer solution, pH = 7.00 (18:1), rt, 80%; (j) oxone, CH_2Cl_2/MeOH/phosphate buffer (pH 9.2)/acetone (1:4:2:0.3), 0 °C, 90%.

Scheme 5



of the adjacent substituent.[8] In the case at hand, it was best achieved by conversion of **14** to its bisthiocarbonate analogue **15**, followed by a free-radical-mediated (Barton−McCombie[9]) cleavage. This sequence led to **16** and, shortly thereafter, to the fused iodolactone **17** en route to **18**.[10] Following traditional protocols, first codified by Grieco,[11] the α-methylene lactonic dienophile **20** was obtained via its hydroxymethyl precursor, **19**, in high yield.

With compound **20** now available via a stereocontrolled route, the synthesis entered its terminal phase. Fortunately, cycloaddition of **20** with **21** occurred quite smoothly. Workup, as shown, led to unraveling of the system with formation of spiroenone **22**. As the synthesis was concluded, this assignment was secured crystallographically (vide infra). The keto group at the future C_9 was subjected to methylenation, as shown (see compound **23** in Scheme 4). In principle, this homologation might be useful in fashioning the tertiary alcohol at C_9. Moreover, we were experiencing difficulties in distinguishing the ketonic and lactonic carbonyl groups, with respect to selective reduction of the latter. With the keto group protected, uncomplicated reduction of the lactone was enabled, paving the way for smooth acetalization between carbons 3 and 15 (see compound **24**). Chemospecific dihydroxylation of the exomethylene group occurred smoothly but furnished a mixture of C_9 hydroxy epimers. Accordingly, the diol was oxidatively cleaved, providing enone **26**. The methylene function at C_9 had in essence served as a blocking group for the C_9 ketone. Nucleophilic methylation was accomplished through the action of methyl lithium and ceric chloride,[12] as shown, in 95% yield with 6:1 stereoselection in the desired sense. Higher ratios of diastereoselection could be achieved (16:1), though in reduced yield, with methylmagnesium bromide (73%). It seems that the stereoselection favors attack of the nucleophile from the axial face, wherein the sp^3 spiro center serves as an equatorially based conformational lock. The total synthesis of spirotenuipesine A (**1a**) was completed upon removal of the PMB group, as shown. In addition to the congruencies of the spectral properties with those of natural product, our assignments are secured by a crystallographic determination of fully synthetic **1a**. Parenthetically, we could convert **1a** to **1b** following a reported protocol.[2]

In summary, the RCM route to **10** was gratifyingly straightforward (three steps rather than nine steps). The use of the α-methylene lactone dienophile (see **20**) with diene **21** indeed provided a stereoselective route to the desired spirocyclic system.[13,14] The nucleophilic methylation controlled by an apparent conformational lock also proceeded with strong stereocontrol. In Scheme 5, we emphasize the teaching message of the interplay between the Claisen and cyclopropane routes. Consider common substrate **28**. In the Claisen route, this starting material undergoes an ene-like carboxymethylation (see **29**). Subsequently, through the medium of formal oxylactonization, **30** is produced. In net terms, there has been accomplished an equivalent of *cis*-hydroxycarboxymethylation (see **30**). However, the relationship between the lactone and the resident OR^2 is not specified. By contrast, the tethered cyclopropanation route leads to **31**. Site-specific vicinal reductive cleavage produces again overall *cis*-hydroxycarboxymethylation (see **31**) *with the important proviso that the cis-bridgehead substituents are syn to* OR^2.

At the biological level, the very concise stereocontrolled total synthesis enables the study of the bio-utility of these compounds, as well as their mechanisms of action. Such collaborative studies are in progress.

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Supporting Information Available: Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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