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Natural Product Synthesis

Total Synthesis of Paecilomycine A**

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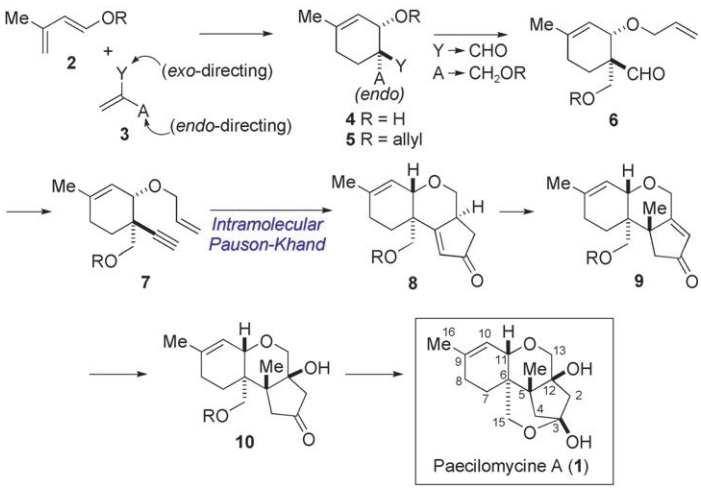
Our group is interested in developing, for mechanistic and efficacy evaluations, small-molecule natural product (SMNP)-derived agents that are of value in the treatment of neurological diseases.[1] Not being a de novo SMNP discovery group, we rely on total synthesis to gain access to the SMNP motif. Molecular "editing" of the parent compound through diverted total synthesis, as opposed to conducting "post-fact" chemistry on the SMNP itself, allows a much broader survey of molecular space to be carried out. One of our targets in the neurodegenerative disorder area is non-peptidyl agents,[2] which can manifest the equivalent of neurotrophic activity. For instance, we described the total synthesis of scabronine G[3] and the corroboration of its claimed neurotrophic activity through enhancement of the expression levels of nerve growth factor (NGF). Some promising analogues have been synthesized as a result of that effort.

Recently, we took note of the isolation and structure assignments of several paecilomyces tenuipes terpenoids from *Isoria japonic*a.[4] The report described that compound **1** (paecilomycine A), at 10 nM, is capable of fostering neurite outgrowth in PC_{12} cells, apparently by enhancing the expression levels of neurotrophic factors in previously conditioned human astrocytoma cells. Also noted was the claim that paecilomycine A (**1**) is substantially more active than scabronine G in enhancing NGF levels. The emergence of an interesting conceptual framework to assemble **1** in the laboratory engendered a total synthesis program. We describe herein an inaugural total synthesis of racemic **1** during which we gained some potentially valuable insights pertinent to the Diels–Alder reaction owing to several early setbacks in our efforts.[5]

We considered paecilomycine A (**1**), particularly in the juxtapositioning of carbon atoms C3, C12, and C15, as reflecting a β-aldol derivative masked as the hemiacetal of a C3 ketone, with a formal primary alcohol at C15. At the planning level, this line of thought led us back to hypothetical structure **9** (Scheme 1). As we anticipated potential vulnerabilities in the formal β-aldol sector within an obvious intermediate **10**, the decision was made to install the hydroxy group at C12 fairly late in the program (see **9**→**10**). We entertained another retrosynthetic simplification, that is, that **9** might be derived from a thus-far unspecified alkylation course (**8**→**9**) in which an important stereochemical determinant is installed at C5. It was further conjectured that, in principle, an intramolecular Pauson–Khand reaction[6] conducted on substrate **7** might lead to the desired intermediate **8**. We were not unmindful of the fact that the projected Pauson–Khand reaction would be creating a 6:5 rather than the more traditional 5:5 fusion motif and that it must occur vicinally to the neopentylic C6 center. Indulging this line of thought still further, we envisioned **7** as arising by allylation of an alcohol precursor following appropriate stereochemical management of the functional groups already in place in hypothetical **4**.



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

In studying the patterns of **6**, one can hardly fail to take note of its cyclohexenol moiety in the form of an allylic alcohol corresponding to carbon atoms C9, C10, and C11 of target structure **1** (with the ethereal oxygen serving as position 1). At this stage in the planning process, the possibility of a Diels–Alder strategy to reach **6** virtually imposed itself. Needless to say, there would be an issue of stereochemistry to be transacted in ensuring the required relationship of the allylic ether and the quaternary center

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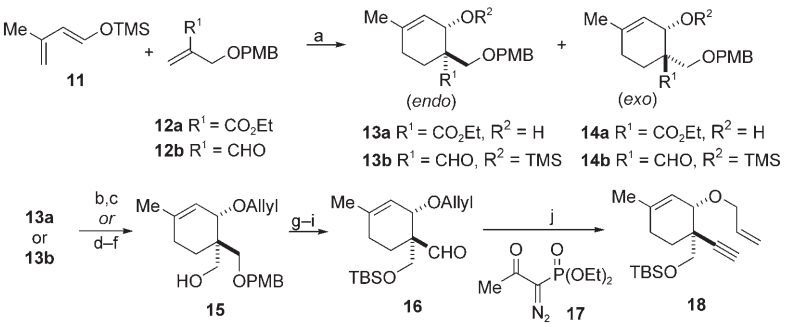
(corresponding to the eventual C6 center). These thoughts are presented in a forward direction in Scheme 1. While the gestalt implied in Scheme 1 seemed appealingly concise, some significant difficulties arose in the more demanding world of experimental reality whose solution, in the end, enhanced the teaching dimension of the experience.

Focusing on the generic potential Pauson–Khand substrate **7**, our initial bias was that the alkynyl group would be fashioned from an aldehyde. This avenue of thought led back to **6**. If, however, **6** were to arise from a Diels–Alder reaction of diene **2** and **3**, an obvious problem presents itself. Thus, the aldehyde function in **6** is stereochemically situated such as to require an *exo*-selective cycloaddition reaction from an *E*-configured generic **2**. Given the difficulties in finding highly activating Diels–Alder groups which are also *exo*-selective, it was decided to derive the protected hydroxymethyl function at C6 from what was the *endo*-selective functional group in **3.** Conversely, the aldehyde functional group identified for eventual conversion into the acetylene group required for the Pauson–Khand reaction would have actually been derived from the *exo*-directing function in **3**. Thus, the emerging plan envisioned a "role reversal" in progressing from the opening Diels–Alder phase toward intermediate **6** required for the all-critical Pauson–Khand strategy. We anticipated that, in essence, the umpolung-like[7] reversal could be accomplished by redox-type adjustment of functional groups to reach **6**. The acetylene function in **7** would have been derived from the aldehyde group of **6** which, following the role reversal, would have been derived from the *exo*-directing function of **3**.

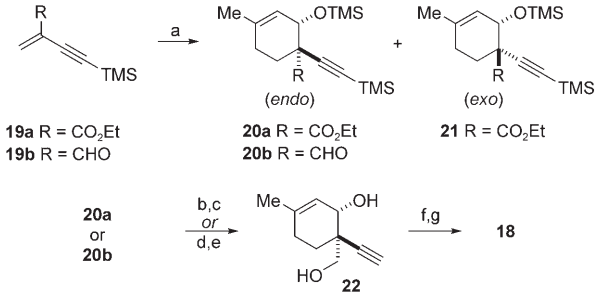
We first studied the Diels–Alder reaction of **11**[8] and **12a**,[9] each a known compound, under strictly thermal activation (Scheme 2). When the cycloaddition reaction was conducted in toluene at approximately 140 °C, and then followed by deprotection, an 88% yield of a 2:1 mixture of **13a** and **14a** was obtained. It was decided for the moment to use this quick and processible route—albeit of uninspiring selectivity—to provide material for exploration. We were hopeful that if the overall route would be shown to have merit, means would be found to improve upon the poor Diels–Alder *endo*/*exo* ratio. O-alkylation of **13a** proceeded smoothly as shown to afford the allyl ether (Scheme 2). Reduction of the ester group allowed for access to **15**, which was protected as a silyl ether. Deprotection of the PMB group and oxidation of the resultant alcohol to aldehyde was accomplished to give compound **16**. The latter compound proved to be a competent substrate for a Gilbert ethynylation[10] to afford the milestone compound **18**, on which the critical Pauson–Khand reaction could be undertaken.

Before we disclose the route by which paecilomycine A (**1**) was reached from compound **18**, we describe other routes that are considerably more stereoselective in reaching this key intermediate. In this vein, cycloaddition of diene **11** with aldehyde **12b**[11] afforded a 6:1 ratio of *endo* (**13b**) to *exo* (**14b**) products. The former product was converted into alcohol **15** as shown (Scheme 2).[12] Thus, perhaps not surprisingly, the more reactive aldehydo dienophile exhibited greater *endo*:*exo* selectivity owing to the activating aldehyde function (see generic structure **3**, Scheme 1).



Scheme 2. Reagents and conditions: a) 1) Toluene, 145 °C, 48 h; 2) TBAF, THF, 10 min, 88% (**13a**/**14a** = 2:1) or benzene, 80 °C, 22 h, 87% (**13b**/**14b** = 6:1); b) allyl bromide, NaH, TBAI, HMPA, THF, 0 °C to 23 °C, 85%; c) DIBAL, CH_2Cl_2, 0 °C, 100% (from **13a**); d) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*BuOH, H_2O, 2-methyl-2-butene, 99%; e) allyl bromide, NaH, TBAI, HMPA, THF, 61% (+8% diastereomer); f) DIBAL, CH_2Cl_2, 0 °C, 100% (from **13b**); g) TBSCl, imid, CH_2Cl_2, 100%; h) DDQ, CH_2Cl_2, 84%; i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 90%; j) **17**, K_2CO_3, MeOH, 85%. TMS = trimethylsilyl; PMB = *p*-methoxybenzyl; TBAF = tetra-*n*-butylammonium fluoride; TBAI = tetra-*n*-butylammonium iodide; HMPA = hexamethylphosphoramide; DIBAL = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; imid = imidazole; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DMSO = dimethyl sulfoxide.

Seeking still greater *endo*:*exo* selectivity and a higher level of convergence, we examined compound **19a**[13] as a potential dienophile. In the event, an approximately 10:1 ratio of *endo* (**20a**) to *exo* (**21a**) products was obtained (Scheme 3). Remarkably, the resident ethynyl function had conferred far higher *endo* selectivity upon the ester group than was the case with dienophile **12a**. Once again, the cycloadduct could readily be converged, as shown, with previously encountered intermediates. Finally, in this regard, even higher *endo*:*exo* stereoselectivity and ultimate synthetic convergence followed from the reaction of aldehyde **19b**[14] with diene **11**, leading to **20b** with greater than 20:1 selectivity.[15] The improvement in *endo*:*exo* selectivity in the presence of the acetylenic group provided an unexpected dividend. Note also that the conditions for effective non-catalyzed cycloadditions with **11**



Scheme 3. Reagents and conditions: a) **11**, CH_2Cl_2, 23 °C, 3 h, 86% (*endo*/*exo* > 10:1) or **11**, CH_2Cl_2, 0 °C, 0.5 h, 58% (*endo*/*exo* > 20:1); b) $LiAlH_4$, THF, 0 °C; c) K_2CO_3, MeOH, (85%, two steps from **20a**); d) $NaBH_4$, MeOH, 0 °C; e) K_2CO_3, MeOH, (72% two steps from **20b**); f) TBSCl, imid, CH_2Cl_2, 89%; g) allyl bromide, NaH, DMF, 70%. DMF = *N*,*N*-dimethylformamide.

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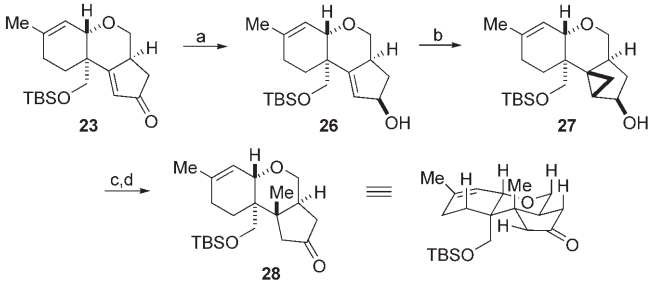
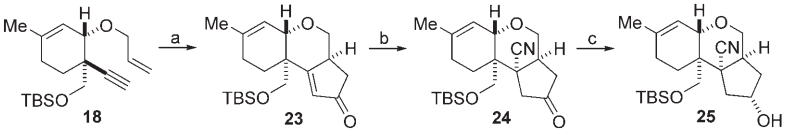
were simplified from 145 °C in the case of **12a** to 0 °C in the case of **19b**.

With excellent routes to **18** well in hand, it was subjected to intramolecular Pauson–Khand reaction at 100 °C under the conditions shown (Scheme 4).[16] A single stereoisomer, **23**, was obtained in 37 % yield. While the yield of the Pauson–Khand reaction was disappointingly modest, the reaction was scalable and the product could be readily purified and advanced to reach paecelomycine A (see below).

One obvious possible pathway to advance from **23** to **1** was frustrated by our inability to achieve under any conditions conjugate nucleophilic methylation by using cuprate reagents. Momentary encouragement arose when it was found that the corresponding Nagata conjugate cyanation[17] could be accomplished in 63 % yield (see compound **24**). However, X-ray crystallographic analysis,[18] conducted on its derived



Scheme 5. Reagents and conditions: a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 86 % (8 % α-alcohol); b) *n*BuLi, Et_2O, −20 °C and then Et_2Zn, CH_2I_2, benzene, 53 % (11 % **26** + 4 % bis-cyclopropane); c) TPAP, NMO, 4-Å M.S., CH_2Cl_2, 93 %; d) Li, NH_3, THF, −33 °C, 65 % (75 % brsm). TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide; brsm = based on recovered starting material.

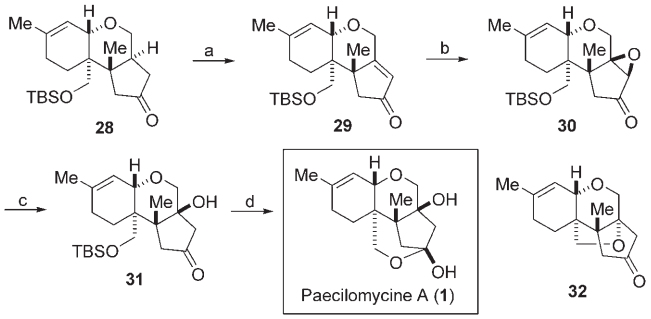


Scheme 4. Reagents and conditions: a) $[Co_2(CO)_8]$, 4-Å M.S., toluene, 23 °C, 2 h, then 100 °C, 24 h, 37 %; b) Et_2AlCN, toluene, 63 %; c) $NaBH_4$, MeOH, 80 %.

alcohol **25** revealed that the cyano group was in the α-position, that is, *syn* to the emerging hydroxymethyl group at the incipient C6 center and the hydrogen atom at C12 (see compound **25**, Scheme 4). While the structure of the Pauson–Khand product **23** had in effect been validated, the stereochemical outcome of the somewhat surprising Nagata reaction seemed to be non-remediable.

To solve the problem of introducing a β-methyl group at C5, we took advantage of an important lesson to be gleaned from the work of Corey and Virgil a decade earlier.[19] The logic of their method exploits local stereochemical biases to reduce a cyclic enone to a particular allylic alcohol. The alcohol then directs stereospecific cyclopropanation in the *syn* sense. In the case at hand, it was applied as follows: The Pauson–Khand enone **23** was reduced under Luche conditions[20] to provide **26**, which underwent cyclopropanation with the in situ generated Furukawa reagent,[21] prepared by addition of diiodomethane to diethylzinc. Under the precisely defined conditions shown (Scheme 5), the desired cyclopropane **27** was obtained along with a small quantity of the starting alcohol **26** and a bis-cyclopropane. Oxidation of the hydroxy group in **27**, followed by dissolving metal reduction of the resultant activated cyclopropane, afforded the cyclopentanone **28** in good yield. The stereochemistry of the angular methyl group was elucidated at this stage by a NOESY experiment, in which we observed NOE enhancement signals between the C14-methyl hydrogen atom and five neighboring hydrogen atoms. The crystal structure eventually obtained on paecilomycine A confirmed the soundness of this analysis (see below).

Completion of the synthesis of paecilomycine A required introduction of a tertiary alcohol at C12 and removal of the silyl protecting group, and ring closure to the hemiacetal (Scheme 6). Ketone **28** was converted into enone **29** by dehydrogenation of the silyl enol ether according to the protocol of Itoh et al.[22] Nucleophilic epoxidation of the resulting enone using hydrogen peroxide and sodium hydroxide[23] occurred *syn* to the angular methyl group (see epoxyketone **30**, Scheme 6). The stereo-



Scheme 6. Reagents and conditions: a) 1) LiTMP, TMSCl, THF, −78 → 0 °C; 2) $Pd(OAc)_2$, CH_3CN, 68 % (71 % brsm); b) aq. H_2O_2, 6 N NaOH, MeOH, 0 °C, 83 % (89 % brsm); c) Li, NH_3, THF, −33 °C, 63 % (24 % **29**); d) HF/CH_3CN (5:95), 86 %. TMP = 2,2,6,6-tetramethylpiperidine.

chemical outcome of this reaction was tentatively assigned on the basis of the assumption that a *cis* ring juncture would be preferred in a [4.3.0] bicyclic ring system. Many attempts to open the epoxide ring in **30** failed due to the susceptibility of its derived β-hydroxyketone **31**. Fortunately, dissolving metal reduction of **30** did provide **31** along with a small amount of enone **29**. Cleavage of the silyl protecting group was also problematic. Thus, attempted deprotection of **31** under basic or acidic conditions using TBAF, trifluoroacetic acid, pyridinium *para*-toluenesulfonate, AcOH, and HF/pyridine,[24] resulted in the formation of the intramolecular Michael product **32**. In the end, the TBS protecting group was successfully removed through the use of hydrofluoric acid in acetonitrile,[25] whereupon the resulting hydroxyketone spontaneously cyclized to furnish (±)-paecilomycine A (**1**; Figure 1) in 86 % yield. The spectral data obtained with our

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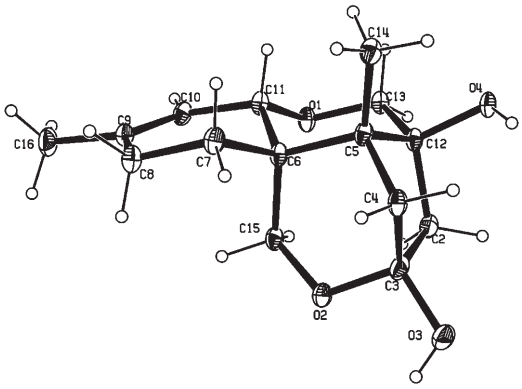

Figure 1. ORTEP representation of paecilomycine A (**1**) with ellipsoids shown at the 20% probability level.

synthetic material were congruent with those obtained from a sample kindly provided by Professor Yoshiteru Oshima (Tohoku University, Japan). The entire set of structured arguments was further validated by a crystallographic investigation of fully synthetic **1**.[18]

In summary, the goal of a total synthesis of paecilomycine A has been accomplished in a highly stereoselective manner. While the yield of the Pauson–Khand reaction in the case of substrate **18** was not unexpectedly modest, the reaction served such a powerful enabling role that, for the moment, its uninspiring yield is survivable. Also capable of remediation, in principle, is that the route leads to racemic **1**. These two chemical matters are being addressed even as the primary emphasis of the project now shifts to the evaluation of the utility, the mechanistic basis, and the potential applicability of the neurotrophic-like action of paecilomycine A.

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