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Enantioselective Formal Total Synthesis of (+)-Aspergillide C

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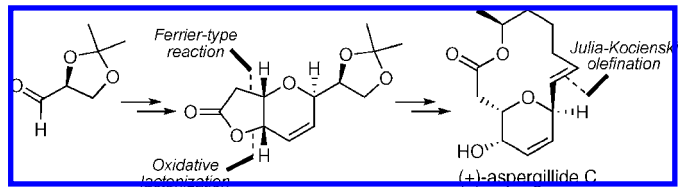
ABSTRACT



An enantioselective formal total synthesis of the cytotoxic macrolide (+)-aspergillide C has been accomplished from (*S*)-(−)-glyceraldehyde acetonide and the Danishefsky−Kitahara diene. Strategic transformations include a hetero Diels−Alder reaction, Ferrier-type addition, and palladium-catalyzed oxidative lactonization to set key stereocenters within the dihydropyran core, followed by fragment coupling via (*E*)-selective Julia−Kocienski olefination.

In 2008, three secondary metabolites, aspergillides A−C (Figure 1), were isolated by Kusumi and co-workers from a marine-derived fungus, *Aspergillus ostianus* strain 01F313, collected off the coast of Pohnpei.[1] Importantly, aspergillides A−C displayed cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.1, 71.0, and 2.0 μg/mL, respectively.

The structures of aspergillides A−C were originally assigned through a combination of spectroscopic methods, and their absolute stereochemistry was determined through Mosher's ester analysis. However, a 2009 synthesis of aspergillides A and B by Uenishi suggested discrepancies in the relative stereochemistry originally assigned for these compounds.[2] Shortly after, Kusumi reported corrected structural assignments for aspergillides A and B via X-ray crystallographic analysis of their C(4) *m*-bromobenzoate ester derivatives.[3] Aspergillides A and B were found to be diastereomeric at C(3) rather than at C(13) as originally proposed. This year, additional synthetic efforts have confirmed the revised structures shown in Figure 1.[4,5]

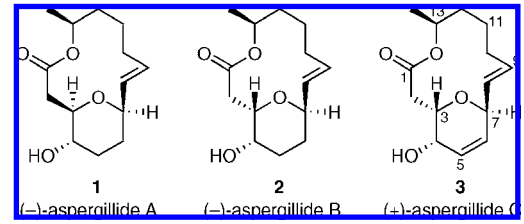


Figure 1. Confirmed structures of aspergillides A−C.

Because of their promising bioactivities and interesting architectures, we also viewed the aspergillides as attractive synthetic targets. Moreover, the aspergillide scaffold could lend itself to diverse structural modifications in projected syntheses of biologically active congeners. In this Letter, we describe our enantioselective approach to the synthesis of

(1) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225–228.
(2) Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192.
(3) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009**, *38*, 384.
(4) Total syntheses of aspergillide B subsequent to ref 2: (a) Liu, J.; Xu, K.; He, J.; Zhang, L.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 5063–5066. (b) Diaz-Oltra, S.; Angulo-Pachon, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783–3785. (c) Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893–1894.
(5) Total synthesis of aspergillide C: Kuwahara, S.; Nagasawa, T. *Org. Lett.* **2009**, *11*, 761–764.

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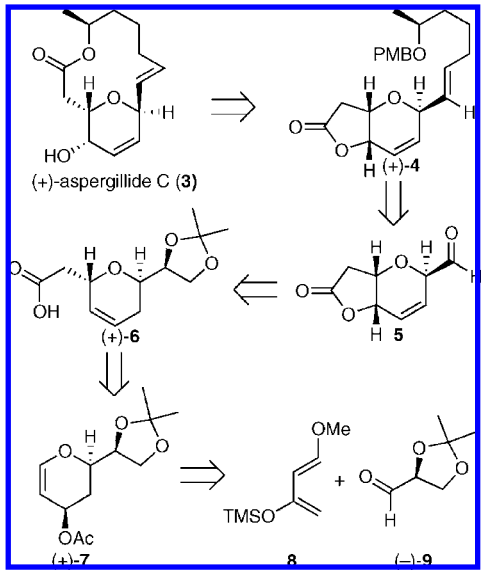
(+)-aspergillide C (**3**) that intersects at a late stage with Kuwahara's recently reported synthesis.[5]

We envisaged that aspergillide C could be reached from lactone (+)-**4** after saponification, protecting group adjustment, and macrolactonization (Scheme 1). In turn, intermediate (+)-**4** could be accessed from aldehyde **5** and a sulfone fragment through *E*-selective Julia−Kocienski olefination. The lactone moiety in **5** could be obtained through palladium-catalyzed oxidative cyclization of carboxylic acid (+)-**6**. The 2,6-*trans* relationship of the dihydropyran ring in (+)-**6** could be realized through Ferrier-type addition of a suitable two-carbon nucleophile onto allylic acetate (+)-**7**, which could be reached from the cycloadduct of diene **8** and optically pure (*S*)-(−)-glyceraldehyde acetonide (**9**).

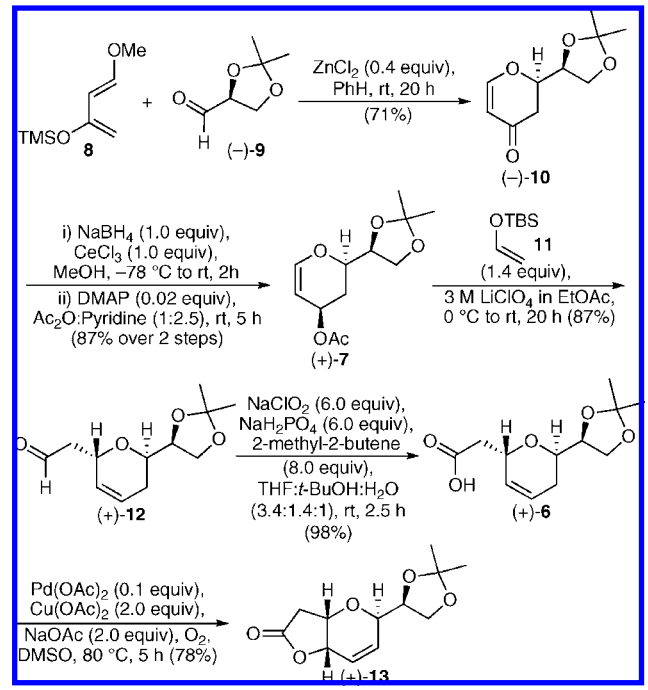
Scheme 1. Retrosynthetic Analysis of (+)-Aspergillide C



The synthesis commenced with a zinc-mediated hetero Diels−Alder (HDA) reaction of (*S*)-(−)-glyceraldehyde acetonide (**9**), prepared from L-(+)-arabinose,[6] and the Danishefsky−Kitahara diene[7] (**8**) to afford dihydropyrone (−)-**10** (Scheme 2). In accord with prior accounts, dihydropyrone (−)-**10** was isolated as a single diastereomer as predicted by Felkin's model, thereby securing the requisite configuration at C(7).[8] Reduction of the carbonyl function in (−)-**10** under Luche's conditions[9] followed by acetylation afforded (+)-**7**.

With the intention of fastening the side chain at C(3) via Ferrier-type addition,[10] the identity of a suitable two-carbon nucleophile was considered. The diastereoselectivity of Ferrier-type additions of carbon-centered nucleophiles onto similar glycal systems can be dependent upon the nature of the nucleophile.[11] While use of a highly reactive silyl ketene acetal would provide a product with the correct oxidation level at C(1), use of a moderately reactive silyl enol ether could provide a greater degree of 2,6-*trans* selectivity.[11] Ultimately, *tert*-butyldimethylsilyl vinyl ether (**11**, Scheme 2)[12] was selected with the expectation that the resultant aldehyde product could be easily oxidized to the requisite carboxylic acid. Initial attempts at effecting the addition with Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_2(O^iPr)_2$, and $Ti(O^iPr)_4$ led to complex product mixtures. Gratifyingly, conducting the reaction in a 3.0 M solution of lithium perchlorate in ethyl acetate[13] at rt afforded the desired aldehyde (+)-**12** in 87% yield.[14] As expected, a subsequent Pinnick oxidation[15] smoothly provided carboxylic acid (+)-**6** in nearly quantitative yield.

Scheme 2. Preparation of Lactone (+)-**13**



With the olefin in glycal (+)-**7** now having migrated after Ferrier reaction from C(3−4) to C(4−5) as shown in acid (+)-**6** and C(1) now at the appropriate oxidation level, an opportunity was at hand to form a key bond via Pd-catalyzed

(6) (a) Baker, S. B. *J. Am. Chem. Soc.* **1952**, *74*, 827–828. (b) MaloneyHuss, K. E. *Synth. Commun.* **1985**, *15*, 273–277.

(7) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808. (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Syn.* **1990**, *7*, 312–315.

(8) (a) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981–1982. (b) Ohmori, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 875–885.

(9) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(10) (a) Ferrier, R. *J. Top. Curr. Chem.* **2001**, *215*, 153–175, and references therein. (b) Ferrier, R. J. *J. Chem. Soc. A* **1964**, 5543–5449.

(11) cf. Paterson, I.; Smith, J. D.; Ward, R. C. *Tetrahedron* **1995**, *51*, 9413–9436.

(12) (a) Srisiri, W.; Padais, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1994**, *59*, 5424–5432. (b) Jung, M. E.; Blum, R. E. *Tetrahedron Lett.* **1977**, *43*, 3791–3794.

(13) (a) Grieco, P. A.; Speake, J. D. *Tetrahedron Lett.* **1998**, *39*, 1275–1278. (b) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59–66.

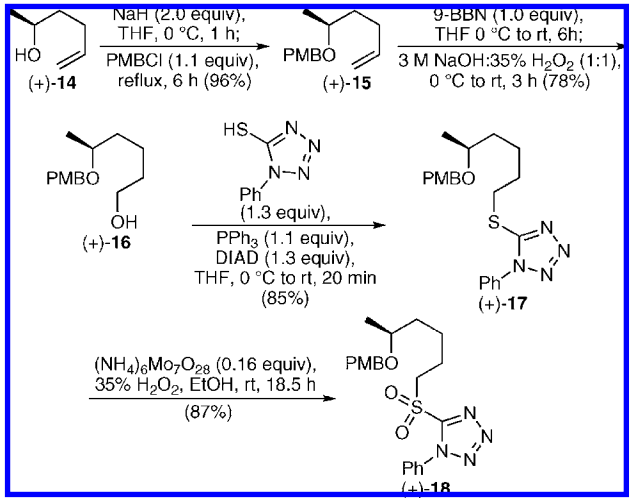
(14) Only trace amounts of what was presumably the 2,6-*cis* isomer could be detected in the ^{1}H HMR spectra of crude reaction mixtures.

(15) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

Wacker-type oxidative lactonization. Such a transformation would achieve three important goals: (i) to introduce the requisite oxygen at C(4) with strict stereocontrol, (ii) to once again make use of an olefin migration to the desired C(5−6) site, and (iii) to utilize the newly formed lactone as an "internal" protecting group during later transformations. Exposure of acid (+)-**6** to the cyclization conditions described by Larock[16] afforded lactone (+)-**13** in 78% yield.

A suitable optically active starting material for the C(9−14) segment of aspergillide C was found in commercially available *S*-(+)-5-hexen-2-ol (**14**, Scheme 3),

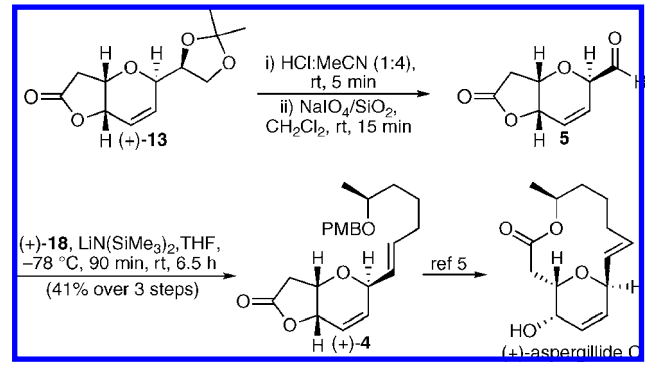
Scheme 3. Preparation of Sulfone Fragment (+)-**18**



which after protection of the alcohol function provided PMB ether (+)-**15**.[17] Hydroboration-oxidation of the terminal olefin in (+)-**15** furnished primary alcohol (+)-**16**. Following the method of Kocienski,[18] a Mitsunobu-type reaction between (+)-**16** and 1-phenyl-1H-tetrazole-5-thiol gave sulfide (+)-**17**, which after oxidation with ammonium heptamolybdate and H_2O_2 afforded sulfone fragment (+)-**18**.

After removal of the acetonide moiety in (+)-**13** and oxidative scission of the resultant vicinal diol with silica-gel-supported $NaIO_4$ in CH_2Cl_2[19] attention was given to fragment coupling of **5** and (+)-**18** via a Kocienski-modified Julia olefination (Scheme 4).[19] After a survey of bases,

Scheme 4. Fragment Coupling via Modified Julia Olefination



solvents, and additives, the use of LHMDS in THF favored the desired *E*-olefin almost exclusively in modest yield, while the use of KHMDS led to considerable erosion of selectivity (2:1 *E*/*Z*) but with similar yield. These results correlate well with those of She and co-workers, who used a Julia tactic in a very recent synthesis of *ent*-aspergillide B.[4a]

The final stage of the synthesis would require hydrolysis of the lactone in (+)-**4**, protecting group adjustment, and macrolactonization. Indeed, during the course of our work, an alternate path to (+)-**4** and its successful elaboration to (+)-aspergillide C by such a sequence was reported by Kuwahara.[5] Our synthetic route to (+)-**4**, obtained in a nine-step longest linear sequence from (*S*)-(−)-glyceraldehyde acetonide in 17% overall yield, now constitutes a formal synthesis. Continued efforts toward the preparation of the remaining members of the aspergillide series are in progress.

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

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