Enantioselective Synthesis of the Cyclopentyl Core of the Axinellamines

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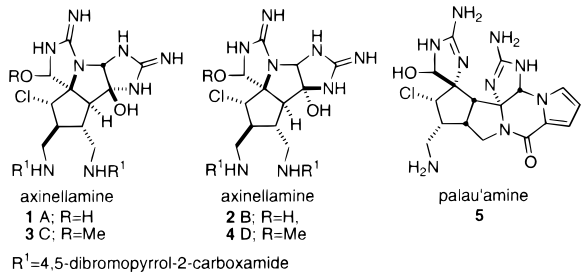
Axinellamines A−D (**1**−**4**) are novel bis-guanidine alkaloids isolated from the marine sponge *Axinella* sp. of which Axinellamines B−D (**2**−**4**) have been shown to possess bactericidal activity against *Helicobacter pylori*, a bacterium implicated in pepticular and gastric cancer.[1] These natural products are noteworthy for the structural complexity of the polycyclic framework incorporating fused and spirocyclic ring systems. Moreover, embedded within these structures is a stereochemically complex and densely functionalized cyclopentyl core that presents a daunting synthetic challenge. A similarly substituted cyclopentane core can be found in palau'amine **5** which critically differs from that of **1**−**4** in the relative stereochemical relationships of the pendant functionality.[2] Palau'amine **5** has attracted considerable attention due to its potent antibiotic, immunosuppressive, and cytotoxic properties (Chart 1).

Progress toward the synthesis of the palau'amine core has been reported in an elegant model study by Overman;[3] however, a fully functionalized cyclopentane intermediate en route to either **5** or axinellamines A−D (**1**−**4**) has not been published. We herein report an *enantioselective* synthesis of the fully functionalized cyclopentyl core **25** of axinellamines A−D (**1**−**4**) from *racemic* spiro[2.4]hepta-4,6-diene-1-methanol **6**.[4]

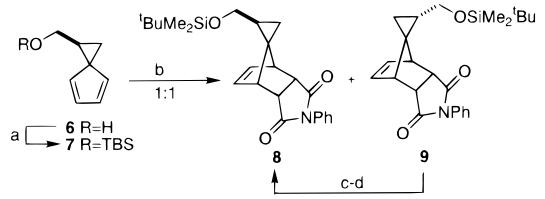
The synthesis commenced with silylation of inexpensive and easily prepared racemic spiro[2.4]hepta-4,6-diene-1-methanol **6** with *tert*-butyldimethylsilyl chloride (100%). The highly exothermic Diels−Alder reaction of **7** with *N*-phenylmaleimide in CH_2Cl_2 at 0 °C then gave a 1:1 mixture of the two endo adducts **8** and **9**. Diastereomer **8**[5] preferentially crystallized from cyclohexane, and the balance of material was recovered following filtration and evaporation of the mother liquor. When a solution of the recovered diastereomer **9** in chlorobenzene (ClPh) was subsequently heated to reflux, **9** underwent retro-cycloaddition and Diels−Alder cycloaddition to regenerate the 1:1 mixture of endo isomers **8** and **9** from which **8** could be crystallized as before. Three such cycles furnished **8** as a single diastereomer from a 200-g scale reaction in 74% yield (Scheme 1).

Desilylation of **8** (99%) and conversion of the resulting alcohol **10** to the iodide **11** (93%) was followed by radical-induced cyclopropane-ring fragmentation using a modification of Nakamura's conditions for dehalogenative hydroxylation (Scheme 2).[6] Iodide **11** was dissolved in benzene and vigorously aerated at 23 °C while Bu_3SnH was added over 2 h. After another 15 h, the addition of hexanes led to precipitation of **12** in 72% yield as a white solid that was free of organotin contamination. An additional 14% of **12** could be obtained by purification of the filtrate. After protection of **12** ($^tBuMe_2SiCl$, 92%), imide **13** was converted to anhydride **14** in 95% yield (two steps) by a sequence involving imide hydrolysis (1M LiOH, THF) to an acid-anilide, followed by dissolution of this unpurified product in toluene at 23 °C to allow spontaneous cyclization with expulsion of aniline. Following acidic workup, the isolated anhydride **14** was spectroscopically pure by ^1H NMR.[7]

Chart 1

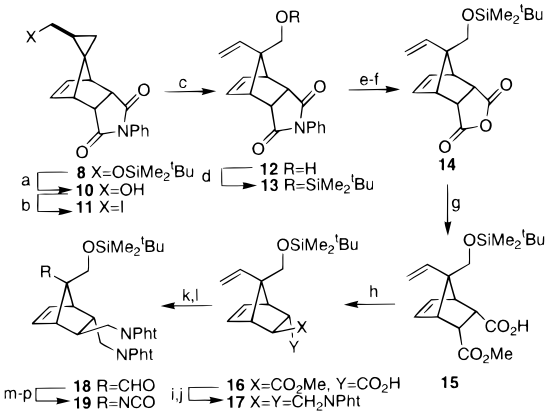


Scheme 1[a]



[a] a) $^tBuMe_2SiCl$, imidazole, DMF, 100%; b) CH_2Cl_2 then crystallize from *c*-C_6H_{12}; c) ClPh Δ; d) crystallize from *c*-C_6H_{12}; 74% (b + 3 cycles of c and d).

Scheme 2[a]



[a] a) HF−CH_3CN/THF (4:1), 99%; b) I_2, PPh_3, imidazole, CH_2Cl_2, 93%; c) Bu_3SnH, air, PhH, 86%; d) $Me_2{}^tBuSiCl$, Et_3N, DMF, 92%; e) 1 N LiOH, THF; f) MePh, 95% (2 steps); g) quinine (1.1 equiv), MeOH (3 equiv), CCl_4, MePh (93% ee), 100%; h) LDA (5 equiv), Et_2O, 0 °C then 1 N $NaHSO_4$, 73% (2 steps); i) $LiAlH_4$, Et_2O, 81%; j) phthalimide, DEAD, PPh_3, THF, 88%; k) OsO_4 (0.05 equiv), $(DHQD)_2Pyr$ (0.05 equiv), NMO (3 equiv), ^tBuOH, 98%; l) $NaIO_4$, K_2CO_3 (3 equiv), THF/H_2O (1:1), 92%; m) $NaClO_2$, DMSO, $^tBuOH/H_2O$ (4:1), pH = 4; n) $(COCl)_2$, CH_2Cl_2; o) NaN_3, DMSO; p) PhH Δ, 67% (4 steps).

(1) (a) Urban, S.; Leone, P. D.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.

(2) (a) Kinnel, R. B.; Gehrken, H. P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (b) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

(3) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159.

(4) (a) Starr, J. T.; Baudat, A.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 5675. (b) Ledford, B. E., Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811. (c) Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R. *Tetrahedron Lett.* **1975**, 1161.

(5) Determined by nOe difference ^1H NMR analysis.

(6) (a) Sawamura, M.; Kawaguchi, Y.; Nakamura, E. *Synlett* **1997**, 801. (b) Sawamura, M.; Kawaguchi, Y.; Sato, K.; Nakamura, E. *Chem. Lett.* **1997**, 705. (c) Nakamura, E.; Sato, K.; Imanishi, Y. *Synlett* **1995**, 525. (d) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.

(7) Analytically pure samples could be readily obtained by crystallization from cyclohexane.

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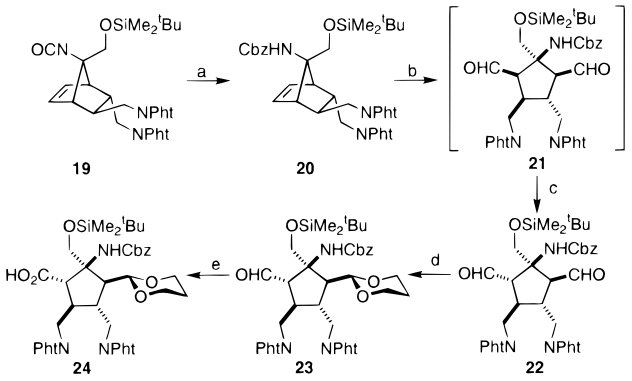
Scheme 3



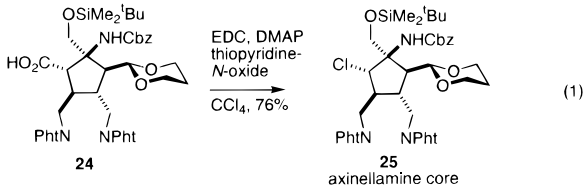
a) BnOH (1.2 equiv), BuLi (1.2 equiv), THF, 0 °C, 76%; b) O_3/O_2, CH_2Cl_2, −78 °C then PPh_3 (1 equiv); c) PPh_3 (0.2 equiv, 16 h) or K_2CO_3 (3 equiv, 0.5h), 86%; d) 1,3-propanediol, Et_2O, PPTS (3 equiv), 59%; e) $KMnO_4$ (1.5 equiv), pH = 7, $^tBuOH/H_2O$ (2:1), 100%.

Up to this point in the route, the synthesis had been conducted with intermediates that were initially racemic (**6**−**11**) and subsequently meso (**12**−**14**). To access the targeted axinellamine core in optically active form, a desymmetrization reaction was required. Thus, utilizing methodology recently reported by Bolm,[8] treatment of **14** with methanol (5 equiv) and quinine (1 equiv) in CCl_4/toluene gave, after workup, methyl ester-acid **15** in 93% ee.[9] Selective C_α-epimerization of the methyl ester (LDA, 5 equiv, Et_2O, 0 °C) gave *trans* acid-ester **16** in 73% yield from **14**.[10]

Reduction of **16** with $LiAlH_4$ gave a diol which was converted to bis(phthalimide) **17** in 71% yield (two steps). Chemoselective cleavage of the monosubstituted olefin in **17** was achieved by treatment of **17** with OsO_4 (0.05 equiv), $(DHQD)_2Pyr$ (0.05 equiv), and NMO (3 equiv) in THF/H_2O to give diastereomeric diols which following treatment with $NaIO_4$ afforded aldehyde **18** (90%).[11,12] This aldehyde underwent oxidation and conversion to the corresponding acyl azide which, without purification, participated in Curtius rearrangement to afford isocyanate **19**. Treatment of **19** with 1.2 equiv of BnOLi in THF at 0 °C then afforded the desired Cbz-protected amine **20** in 76% yield (Scheme 3).

The nearly fully functionalized cyclopentyl core was then revealed by exposure of **20** to ozone, followed by reductive workup (1.2 equiv PPh_3), to give the unexpected *trans*-dial **22**. Careful monitoring of the workup by ^1H NMR spectroscopy revealed that epimerization was observed only in the presence of excess PPh_3, and by strictly limiting the stoichiometry to 1.0 equiv, *cis*-dial **21** could be observed in solution. However, in contrast to *trans*-dialdehyde **22**, which was well-behaved on silica and in subsequent handling, attempts to purify **21** were not successful. Therefore, we chose to proceed with the *trans*-dial **22**; optimization of the workup conditions (K_2CO_3, 3 equiv)[13] to promote clean conversion to the *trans*-dial gave **22** in 86% yield.

The remaining task in completing the axinellamine cyclopentyl core was the stereoselective installation of the chlorine. We envisioned accomplishing this goal via decarboxylation of a Barton ester in the presence of a suitable chlorine donor.[14] Selective protection of the aldehyde syn to the carbamate could be effected by acetalization of **22** with 1,3-propane diol in Et_2O to afford **23** in 59% yield.[15] Aldehyde **23** was then cleanly converted in quantitative yield to carboxylic acid **24** using Masamune's oxidation conditions ($KMnO_4$, ^tBuOH/water, pH = 7).[16]



(1)

Installation of the hindered chlorine was then achieved by treating **24** with EDC (2 equiv), DMAP (0.3 equiv), and 2-thiopyridine-*N*-oxide (1.3 equiv) in rigorously deoxygenated CCl_4 to form the corresponding Barton ester, followed by stirring the solution for 12 h to allow spontaneous homolytic cleavage of the ester, decarboxylation, and then abstraction of chlorine from solvent.

The resulting product **25** was isolated in 76% yield from **23** in >10:1 dr.[17] That the chlorine was installed with the desired stereochemistry in the major isomer was determined by nOe experiments showing reciprocal enhancements between the chloromethine C−H and carbamate N−H confirming the fully functionalized cyclopentyl core **25** of axinellamines A−D **1**−**4** had been synthesized.

We have described the first route to the fully functionalized cyclopentyl core found in the axinellamines A−D **1**−**4**. The route commences with the racemic starting material, spiro[2.4]hepta-4,6-diene-1-methanol **6**, and proceeds through racemic (**6**−**11**) then meso (**12**−**14**) intermediates to an optically active final product **25**. This strategy takes maximal advantage of an inexpensive, readily available racemic starting material by converting it to a meso intermediate and then employing a desymmetrization reaction at an advanced stage. Studies are currently underway to convert **25** to the axinellamines and will be reported in due course.

Acknowledgment. We thank Professor Volker Gramlich of the ETH-Z Laboratory of Crystallography for X-ray crystallographic analyses on compound **16**. We thank the National Science Foundation for a predoctoral fellowship for J.T.S. This research has been supported by an award from the Packard Foundation, Swiss National Science Foundation, as well as generous support from Merck, Astra-Zeneca, and Hoffman LaRoche.

Supporting Information Available: Experimental details and characterization for key intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195.

(9) The enantiomeric excess was determined by preparation of the amide derived from (*R*)-(+)-α-phenethylamine and integration of the methyl doublets in the ^1H NMR spectrum.

(10) The structure of **16** was determined by X-ray diffraction analysis, confirming the stereochemical outcome of cyclopropyl carbinyl radical fragmentation (**11** → **12**), methanolysis (**14** → **15**), and C_α-epimerization (**15** → **16**).

(11) Although the use of $(DHQD)_2Pyr$ as a ligand for osmium imparted minimal diastereoselectivity, its use was necessary for achieving the desired chemoselectivity in the dihydroxylation step.

(12) Schroder, M. *Chem. Rev.* **1980**, *80*, 187 and references therein.

(13) (a) AM1 minimization of simplified models of **21** and **22** on PC-Spartan Pro indicated a 3.1 kcal/mol preference for the *trans*-dialdehyde. (b) For use of K_2CO_3 in a similar epimerization see: Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *J. Org. Chem.* **1999**, *64*, 5413.

(14) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(15) The selectivity for **23** in the acetal-forming reaction was established by reciprocal NOE enhancements between the acetal methine proton and the carbamate N−H proton as well as the aldehyde α-proton and the carbamate N−H in the mono aldehyde **23**. AM1 calculations indicate that there is only a minor energy difference (0.3 kcal/mol) between the heats of formation of the two possible acetals. We speculate that the reaction is under kinetic control by factors that are unclear presently. Studies are underway to provide insight into the observed group selectivity.

(16) Abiko, A.; Roberts, J. C.; Takewasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

(17) AM1 minimization of simplified models of **25** and its diastereomer on PC-Spartan Pro indicated a 1.3 kcal/mol preference for the desired chlorine stereochemistry. Diastereomer ratio was determined by ^1H NMR.