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3-4′-Bipiperidines via Sequential [4 + 4]−[3,3]−Retro-Mannich Reactions

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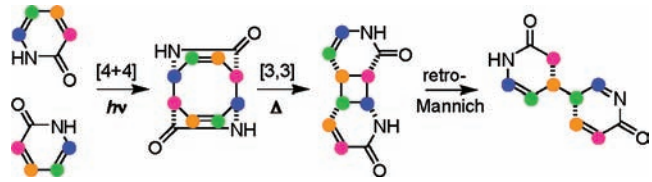
ABSTRACT



An approach to assembling unsymmetrically coupled piperidines is described, involving initial [4 + 4] photocycloaddition of 2-pyridones, followed by Cope rearrangement and retro-Mannich reaction. In these reactions, four stereogenic centers set during cycloaddition are relayed or erased during the subsequent steps. Two methods for retro-Mannich reaction are demonstrated.

Piperidine rings, unsymmetrically coupled at C3 and C4′, are a structural motif widely distributed among alkaloids. The tetra- and pentacyclic examples in Figure 1 are archetypes,[1] and important biological activities have been found for a number of these structures.[2] Natural products containing this ring system, but with additional points of cyclization between the piperidines, are also known.[3] Biosynthesis of these alkaloids has been proposed to involve dimerization of dihydropyridines, and biomimetic studies have confirmed the viability of this pathway.[4] Among the challenges presented by these molecules is the control of the stereochemistry where the piperidine rings are joined. Synthesis also has the potential to define the unknown 3′ stereocenter of the saraines.[5]

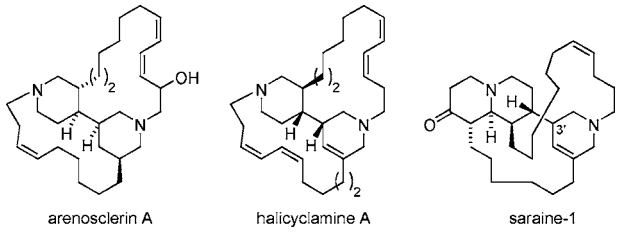


Figure 1. Coupled piperidine natural products.

We report here a novel method for assembling these structures from aromatic 2-pyridones, beginning with two efficient pericyclic reactions that set and then migrate the key stereogenic centers.

Pyridones such as **1** (Scheme 1) are commercially available or easily prepared and, while relatively unreactive in thermal cycloadditions, will undergo [4 + 4]-photodimerization under

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(1) Torres, Y. R.; Berlinck, R. G. S.; Magalhaes, A.; Schefer, A. B.; Ferrieira, A. G.; Hajdu, E.; Muricy, G. *J. Nat. Prod.* **2000**, *63*, 1098–1105. Jaspars, M.; Pasupathy, V.; Crews, P. *J. Org. Chem.* **1994**, *59*, 3253–3255. Guo, Y. W.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1996**, *52*, 14961–14974.

(2) Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C.; Hooper, J. N. A. *Tetrahedron* **1996**, *52*, 9111–9120.

(3) Tsuda, M.; Inaba, K.; Kawasaki, N.; Honma, K.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 2319–2324. de Oliveira, J. H. H. L.; Grube, A.; Koeck, M.; Berlinck, R. G. S.; Macedo, M. L.; Ferreira, A. G.; Hajdu, E. *J. Nat. Prod.* **2004**, *67*, 1685–1689. Lebrun, B.; Braekman, J.-C.; Daloze, D.; Kalushkov, P.; Pasteels, J. M. *Tetrahedron Lett.* **1999**, *40*, 8115–8116.

(4) Gil, L.; Baucherel, X.; Martin, M. T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, *36*, 6231–6234.

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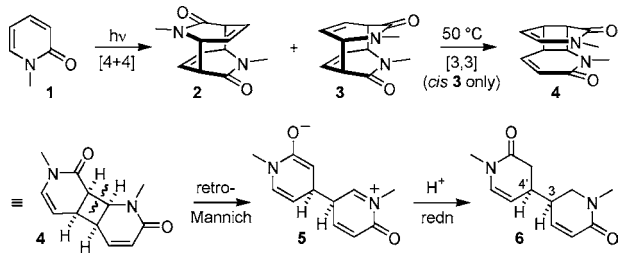
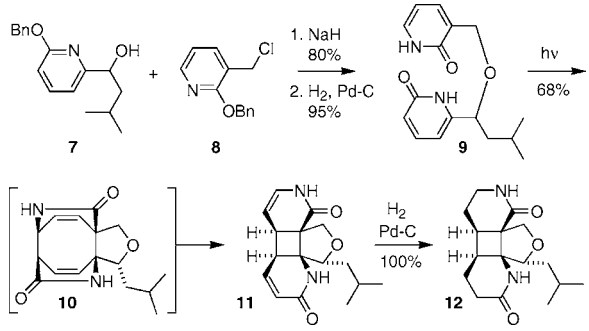
Scheme 1. [4 + 4]-Cycloaddition−Cope Rearrangement−Retro-Mannich Sequence



a rather broad set of conditions, including the use of sunlight.[6] The [4 + 4]-photocycloaddition of two 2-pyridones proceeds with a high degree of solvent-insensitive, head-to-tail regioselectivity and sets four new stereogenic centers. Stereoselectivity can be more variable, with both *trans* **2** and *cis* **3** cycloadducts observed, and methods have been developed for selection of either isomer.[7] These cycloadducts are quite strained, and the *cis* isomer **3** of this functionalized 1,5-cyclooctadiene will undergo a [3,3]-rearrangement at 50 °C to quantitatively yield divinylcyclobutane **4**.[8] Notably, the head-to-tail regioselectivity of the cycloaddition leads to a Cope rearrangement product in which one bond of the cyclobutane of **4** is flanked by an amide nitrogen and an amide carbonyl. It was therefore anticipated that a retro-Mannich reaction[9] of **4** might give a coupled piperidine product **6**, with defined stereochemistry at the 3- and 4′-positions.

We have explored this reaction sequence using the model system **9** (Scheme 2), readily prepared from alcohol **7** and

Scheme 2. *cis*-Selective [4 + 4]-Photocycloaddition and Cope Rearrangement



chloropyridine **8**. Williamson etherification followed by hydrogenolysis of the benzyl ethers yields **9**. The isobutyl group of **7** plays three roles in this study: increasing the solubility of the bis-2-pyridone **9** in nonpolar solvents, controlling relative stereochemistry during the cycloaddition, and providing a stereochemical reference center for the cyclobutane cleavage reaction. Photocycloaddition of **9** in toluene using a medium-pressure mercury lamp leads to a completely *cis*-selective cycloaddition producing **10**. The *cis* stereoselectivity of the cycloaddition stems from the formation of an intermolecular hydrogen bonded dimer of **9**.[7c] The single stereogenic center of **9** was expected to control the four new stereocenters of **10** by adopting a pseudoequatorial conformation on the tether during the cycloaddition. When the photochemistry was performed in the absence of ice-cooling, cyclobutane **11** was obtained directly, in 68% yield, without the need for isolation of cyclooctadiene **10**. In principle, the electronically very different alkenes of **11** could be reduced selectively, but for the purposes of this model system, both alkenes were hydrogenated to give **12**. The stereogenic centers of the rearrangement product **11** were confirmed with an X-ray crystal structure of **12** (see Figure 2).[10]

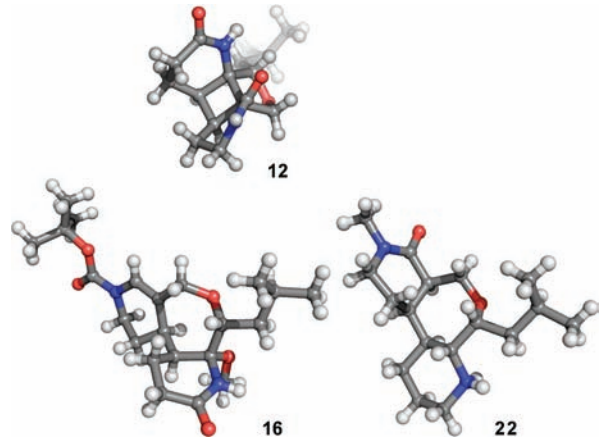


Figure 2. Crystal structures of **12**, **16**, and **22**.

Initially the retro-Mannich reaction was expected to involve simple treatment with a suitable base, but **12** proved to be inert to a variety of basic conditions. The secondary amides were, therefore, modified to promote cleavage, and their substantially different steric environment led to straightforward selectivity. Treatment of **12** with di-*tert*-butyl dicarbonate gave a single derivative, **13** (Scheme 3).[11] The activated carbonyl was then reduced with lithium borohydride, yielding aminal **14**. This sensitive structure underwent

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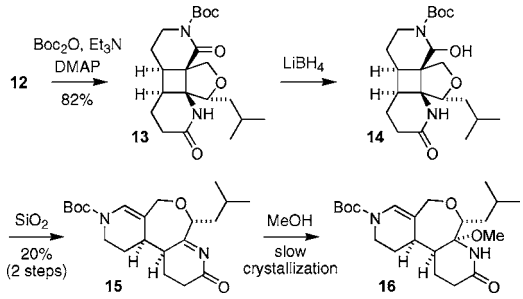
(7) (a) Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597–3599. (b) Sieburth, S. McN.; McGee Jr., K. F.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587–588. (c) Sieburth, S. McN.; McGee, K. F. J. *Org. Lett.* **1999**, *1*, 1775–1777.

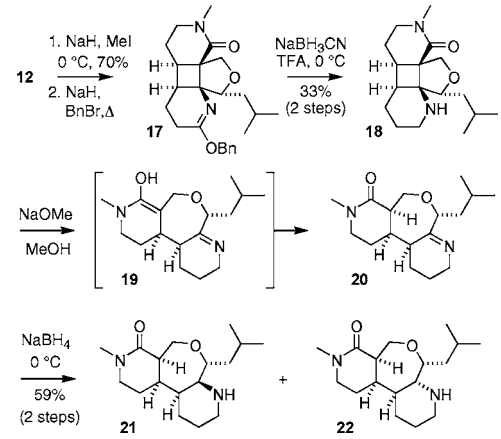
(8) Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187–1191.

(9) (a) Schauble, J. H.; Hertz, E. *J. Org. Chem.* **1970**, *35*, 2529–2532. (b) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836–4842. (c) Schell, F. M.; Cook, P. M. *J. Org. Chem.* **1984**, *49*, 4067–4070. (d) Winkler, J. D.; Scott, R. D.; Williard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 8971–8975. (e) Risch, N.; Langhals, M.; Hohberg, T. *Tetrahedron Lett.* **1991**, *32*, 4465–4468. (f) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229–231. (g) Kwak, Y.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 7429–7430. (h) Aitken, D. J.; Gauzy, C.; Pereira, E. *Tetrahedron Lett.* **2004**, *45*, 2359–2361. (i) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081–1084.

Scheme 3. Boc-Activation of a Lactam and Reduction−Solvolysis Retro-Mannich



Scheme 4. Alternative Retro-Mannich Ring Opening



retro-Mannich reaction under a variety of conditions, including silica gel chromatography. Stirring **14** with silica gel suspended in a methanol−methylene chloride mixture gave the acyl-imine-enamide **15**. The enolizable nature of all three stereogenic centers in **15** made their preservation uncertain, and the flexibility of this structure made NMR determination of its structure problematic. A crystal structure of **15**, grown from methanol, however, confirmed that the stereochemical relationship of these stereocenters was intact, as well as formation of a new stereocenter resulting from addition of methanol to the acylimine (Figure 2, **16**).[12]

An alternative method for cleaving the cyclobutane also took advantage of the divergent amide reactivities of **12** (Scheme 4). Treatment of **12** with sodium hydride and iodomethane gave N-methylation of the less hindered amide. The hindered nature of the remaining amide is evidenced by the O-benzylation product **17** (2:1 *O*-benzyl:*N*-benzyl), generated with sodium hydride and benzyl bromide. Treatment of **17** with sodium cyanoborohydride reduced the imidate to secondary amine **18**. This amine was stable, but when treated with sodium methoxide, a single product **20** was formed. This product had a new stereogenic center, presumably set by kinetic protonation of **19**. Reduction of the imine **20** with sodium borohydride gave a 5:8 mixture of two amines **21** and **22**. The oxalate salt of **22** provided an X-ray structure that defined the five stereogenic centers resulting from this reaction sequence (Figure 2).[13] Notably, the three stereocenters originating in **12** remained in the same relative configurations in product **22**.

In these reaction paths, a [4 + 4]-photocycloaddition sets four stereogenic centers in **10**, fully controlled by the single stereogenic center of the tether isobutyl group. None of these four new stereocenters remain in the ultimate products **15**, **16**, **20**, **21**, or **22**. Cope rearrangement of the [4 + 4] adduct **10** transfers two of those stereogenic centers to the cyclobutane **11**. The other two stereogenic centers disappear during the retro-Mannich reactions. Nevertheless, in each case one of the stereogenic centers that transiently disappear during the retro-Mannich reaction is reformed with complete stereocontrol (structures **16**, **20**). This control may be a function of the seven-membered ether ring biasing the conformational options during protonation of **19** and the addition of methanol to imine **15**. In the latter case, one can assume a reversible addition to the imine, driven by either thermodynamics or the crystallization, leads to formation of product **16**, whereas in the protonation of the amide enol(ate) **19**, this stereochemical outcome is most likely kinetic in origin. On the other hand, the reduction of imine **20** to give a 5:8 mixture of diastereomers **21** and **22** is more consistent with the absence of stereochemical bias engendered by the seven-membered ring. The crystal structures of **16** and **22** reveal the rather open oxepin conformation (Figure 2).

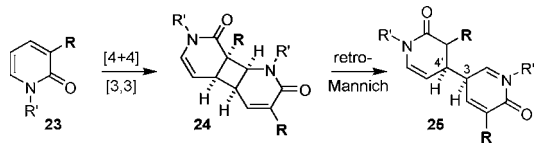
(10) Compound **12**, crystallized from methanol as the hydrate, $C_{16}H_{24}N_2O_3{\cdot}H_2O$, in the rhombohedral space group $R\bar{3}$ with $a = 28.990(2)$ Å, $c = 10.1877(7)$ Å, $V = 7415.0(9)$ Å^3, $Z = 18$, and $d_{calc} = 1.251$ g/cm^3, determined from a 0.30 mm × 0.28 mm × 0.18 mm crystal. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo K$_a$ radiation ($\lambda = 0.71069$ Å) at a temperature of 143 K. Refinement converged to $R_1 = 0.0372$ and w$R_2 = 0.1008$ for 2455 reflections for which $F > 4\sigma(F)$ and $R_1 = 0.0432$, w$R_2 = 0.1053$ and GOF = 1.075 for all 2920 unique, nonzero reflections, and 202 variables. CCDC 714967 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.

(12) Compound **16**, $C_{21}H_{31}N_2O_4$, crystallized from methanol in the triclinic space group P1 with $a = 8.8340(10)$ Å, $b = 10.278(2)$ Å, $c = 13.298(2)$ Å, $\alpha = 90.009(11)°$, $\beta = 106.126(7)°$, $\gamma = 98.122(9)°$, $V = 1147.3(3)$ Å^3, $Z = 2$, and $d_{calc} = 1.087$ g/cm^3, determined from a 0.38 × 0.18 × 0.005 mm crystal. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo K$_a$ radiation ($\lambda = 0.71069$ Å) at a temperature of 143 K. Refinement converged to $R_1 = 0.0459$ and w$R_2 = 0.0999$ for 1925 reflections for which $F > 4\sigma(F)$ and $R_1 = 0.0886$, w$R_2 = 0.1240$ and GOF = 0.984 for all 3553 unique, nonzero reflections, and 269 variables. CCDC 714968 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The oxalic acid salt of compound **22**, $C_{21}H_{38}N_2O_7$, crystallized from ethanol/ethyl acetate in the triclinic space group P1 with $a = 10.3811(13)$ Å, $b = 11.062(2)$ Å, $c = 11.7553(14)$ Å, $\alpha = 109.649(2)°$, $\beta = 93.3740(10)°$, $\gamma = 115.456(2)°$, $V = 1114.6(2)$ Å^3, $Z = 2$, and $d_{calc} = 1.283$ g/cm^3, determined from a 0.40 × 0.23 × 0.06 mm crystal. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo K$_a$ radiation ($\lambda = 0.71069$ Å) at a temperature of 143 K. Refinement converged to $R_1 = 0.0384$ and w$R_2 = 0.0983$ for 2745 reflections for which $F > 4\sigma(F)$ and $R_1 = 0.0541$, w$R_2 = 0.1049$ and GOF = 1.019 for all 3910 unique, nonzero reflections, and 278 variables. CCDC 714969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 5. Dimerization/Rearrangement/Fragmentation of 3-Alkyl-2-pyridones Yielding the Natural Product Substitution



This model study relied on the use of tethered 2-pyridones to induce *cis*-selective [4 + 4]-cycloaddition. Application of the [4 + 4]−[3,3]−retro-Mannich sequence to the substances in Figure 1 would ideally result from a *cis*-selective photodimerization of a single 3-alkyl-2-pyridone **23** (Scheme 5), a sequence that would provide the substitution needed for the natural products in Figure 1. Our investigation of these chemistries is continuing.

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

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