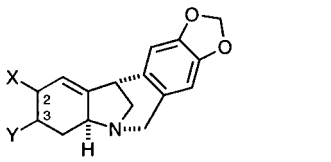
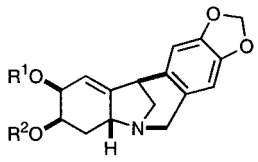
# Application of the 2-Azaallyl Anion Cycloaddition Method to an Enantioselective Total Synthesis of (+)-Coccinine**

William H. Pearson* and Brian W. Lian

The montanine-type alkaloids (e.g., **1**–**8**, Figure 1) form a small class of Amaryllidaceae alkaloids that share the 5,11-methanomorphanthridine ring system[1] and differ primarily



X=β-OMe, Y=α-OH: (–)-montanine **1**
X=α-OMe, Y=α-OH: (–)-coccinine **2**
X=β-OH, Y=α-OH: (–)-pancracine **3**
X=β-OMe, Y=β-OH: (–)-manthidine **4**
X=β-OMe, Y=α-OMe: (–)-manthine **5**
X=β-OH, Y=β-OH: (–)-brunsvigine **6**
X=β-OMe, Y=α-OAc: (–)-*O*-acetylmontanine **7**

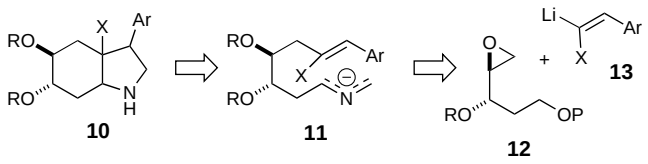


(+)-montabuphine **8**
($R^1$=H, $R^2$=Me)
(+)-coccinine **9**
($R^1$=Me, $R^2$=H)

Figure 1. Montanine-type alkaloids.

in the configurations at the stereocenters and the type of oxygen substitution at C-2 and C-3. The recent isolation of (+)-montabuphine, assigned structure **8**,[2] suggests that both enantiomers of the methanomorphanthridine ring may exist in nature. While Amaryllidaceae alkaloids have in general been the subject of much synthetic effort, the 5,11-methanomorphanthridine class alkaloids has attracted much less attention. Overman and Shim reported the total syntheses of (±)- and (–)-pancracine (**3**),[3] and total syntheses of racemic montanine (**1**), coccinine (**2**), pancracine (**3**), brunsvigine (**6**), and *O*-acetylmontanine (**7**) were published by Hoshino et al.[4] Most recently, Jin and Weinreb reported the enantioselective syntheses of (–)-coccinine (**2**) and (–)-pancracine (**3**).[5] We now describe an enantioselective total synthesis of (+)-coccinine (**9**), the nonnatural enantiomer of (–)-coccinine (**2**), which uses our 2-azaallyl anion cycloaddition methodology[6, 7] as the key step. This represents the first assembly of the 5,11-methanomorphanthridine ring system in the uncommon enantioseries.

For the retrosynthesis (Figure 2) we envisioned the assembly of montanine-type alkaloids from the perhydroindole **10**, which should be available by the intramolecular cycloaddition of the 2-azaallyl anion **11**.[6] Pictet–Spengler cyclization, previously applied by Overman and Shim,[3] would be used to incorporate the methano bridge, and elimination of HX from **10** would form the requisite alkene. The precursor to the

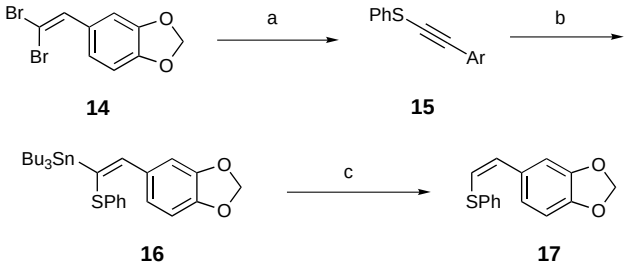


**10** **11** **12** **13**

Figure 2. Synthetic strategy for montanine alkaloids.

anion **11** should be accessible from the epoxide **12** and the vinyllithium compound **13**.[8] The diastereoselectivity of the intramolecular 2-azaallyl anion cycloaddition is still relatively unexplored.[9] On the basis of molecular models, we proposed that anion **11** would produce the isomer of **10** required for a synthesis of (–)-montanine (**1**). As revealed below, an alternate stereochemical outcome which ultimately allowed access to the alternative enantioseries was observed experimentally.

Our synthesis began with the assembly of the vinyllithium precursor **17** (Scheme 1). Piperonal was converted into the



**14** **15** **16** **17**

Scheme 1. Synthesis of the vinyl sulfide **17**: a) *n*BuLi (2 equiv), THF, –78 °C, 1 h, RT, 1.5 h; PhSSPh, THF, –78 °C, 0.5 h, RT, 0.5 h, 78%; b) [Pd($PPh_3$)$_4$] (cat.), $Bu_3SnH$, $C_6H_6$, RT, 14 h; c) *n*BuLi (3 equiv), THF, –78 °C, 0.5 h, sat. aq. $NH_4Cl$, RT, 89% based on **15**.

known vinylidene dibromide **14**[10] with $CBr_4/PPh_3/Zn$.[11] Conversion of **14** into the alkynyllithium compound followed by quenching with diphenyl disulfide produced the alkynyl sulfide **15**. Regioselective hydrostannylation[12] of **15** provided the vinyl stannane **16**, which was best used without purification. Tin–lithium exchange followed by protonation gave the (*Z*)-vinyl sulfide **17** in good overall yield.[13]

The synthesis of the (2-azaallyl)stannane **26** required for the 2-azaallyl anion cycloaddition is shown in Scheme 2. The epoxide **22** needed for coupling with the vinyl sulfide **17** was prepared by the Sharpless asymmetric dihydroxylation method.[14] The known *p*-methoxybenzyl-protected diol **18**[15] was subjected to Swern oxidation, Horner–Wadsworth–Emmons olefination, reduction with diisobutylaluminum hydride, mesylation, and in situ displacement of the chloride substituent[16] to provide the allylic chloride **19**. Asymmetric dihydroxylation of **19** gave the diol **20**,[17] which was converted into the epoxyalcohol **21** with sodium hydride. Mosher's ester analysis of **21** indicated an enantiomeric excess of 88% for this material. Protection of **21** as a benzyl ether provided the desired epoxide **22**. Deprotonation of the vinyl sulfide **17** with *tert*-butyllithium followed by reaction with epoxide **22** in the presence of $BF_3 \cdot OEt_2$[18] afforded the alcohol **23** in good yield with complete retention of the alkene geometry.[19] Methylation of **23** gave **24**, which was selectively deprotected to

[*] Prof. W. H. Pearson, B. W. Lian
Department of Chemistry
University of Michigan
930 N. University, Ann Arbor, MI 48109–1055 (USA)
Fax: (+1) 734-763-2307
E-mail: wpearson@umich.edu

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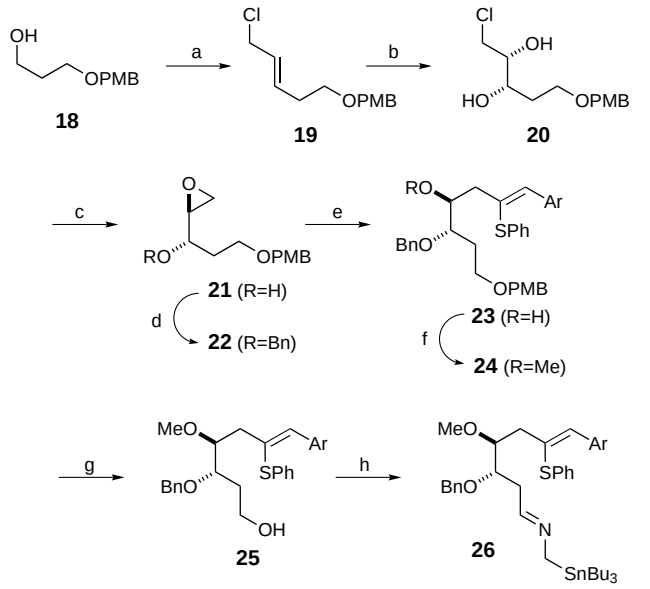
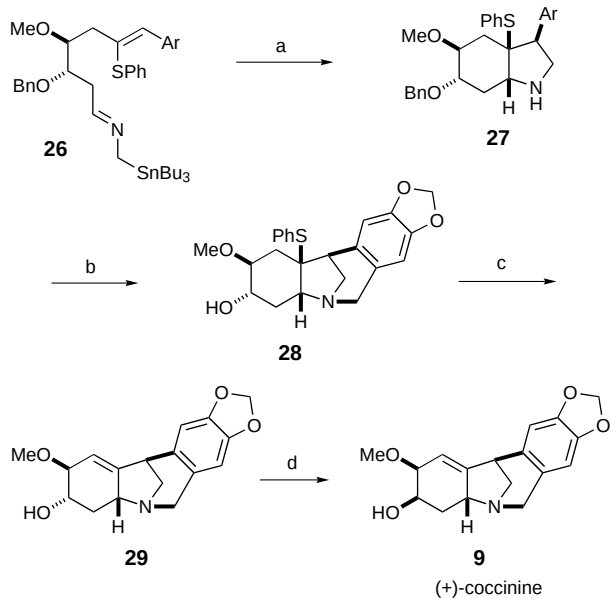



Scheme 2. Synthesis of (2-azaallyl)stannane **26**: a) 1. $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$; 2. $(MeO)_2P(O)CH_2CO_2Me$, NaH, $C_6H_6$, RT, 14 h; 3. $iBu_2AlH$, toluene/THF, 0 °C, 45 min, RT, 30 min; 4. MsCl, $iPr_2NEt$, $CH_2Cl_2$, −23 °C, 45 min, dilute with DMF, add LiCl (2 equiv), RT, 5 h, 41 % based on **18**; b) AD-mix-$\alpha$, THF, $t$BuOH, $H_2O$, $MeSO_2NH_2$, 0 °C, 48 h, 100 %; c) NaH, THF, DMSO, RT, 12 h, 81 %; d) NaH, BnBr, THF, DMSO, 0 °C, 2 h, RT, 24 h, additional portion of NaH/BnBr, RT, 8 h, 82 %; e) **17** (2.8 equiv) + $t$BuLi (2.8 equiv), −78 °C, THF, 15 min, add **22**, add $BF_3 \cdot OEt_2$ (2.8 equiv), −78 °C, 45 min, 80 %; f) NaH, THF, 0 °C, MeI, RT, 14 h, 100 %; g) EtSH (27 equiv), $CH_2Cl_2$, $BF_3 \cdot OEt_2$, −78 °C, then −25 °C, 24 h, 92 %; h) 1. $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, 94 %, or tetrapropylammonium perruthenate (cat.), *N*-methylmorpholine *N*-oxide, 4-Å molecular sieves, $CH_2Cl_2$, RT, 14 h, 78 %; 2. $Bu_3SnCH_2NH_2$, $Et_2O$, 4-Å molecular sieves, RT, 16h, 86 %. Bn = benzyl, Ms = methanesulfonyl, PMB = *p*-methoxybenzyl.

provide the alcohol **25**. Oxidation and condensation with (aminomethyl)tri-*n*-butylstannane[6c] gave the desired (2-azaallyl)stannane **26**.

Without purification, **26** was subjected to tin–lithium exchange at low temperature with *n*-butyllithium (Scheme 3). Quenching the reaction with water provided a single stereoisomer of the perhydroindole **27** in 45 % yield. At this point, the configuration of the three new stereocenters was not known. Pictet–Spengler cyclization of **27** with concomitant removal of the benzyl protecting group gave the 5,11-methanomorphanthridine **28**. Oxidation of the HCl salt of **28** to generate the sulfoxide followed by thermolysis gave **29**, which differed from an authentic sample of (−)-montanine (**1**).[20] The optical rotation of **28** (and all subsequent compounds) was dextrorotatory rather than levorotatory, which provides evidence that the cycloaddition had produced the enantiomeric 5,11-methanomorphanthridine skeleton. Thus, we inverted the alcohol of **29** to produce the nonnatural enantiomer of coccinine. Mesylation of **29** followed by displacement with acetate and saponification provided (+)-coccinine (**9**), which was identical to natural (−)-coccinine (**2**)[20] in all respects ($R_f$ value in thin-layer chromatography (TLC), 500-MHz $^1H$ NMR and 90-MHz $^{13}C$ NMR spectra, and mass spectrum) with the exception of optical rotation [synthetic (+)-coccinine: $[\alpha]_D^{25} = +96$ ($c = 0.05$, EtOH), $[\alpha]_D^{25} = +182.2$ ($c = 0.045$, $CHCl_3$); natural (−)-coccinine: $[\alpha]_D^{25} = -104$ ($c = 0.07$, EtOH), $[\alpha]_D^{25} = -218.2$ ($c = 0.055$, $CHCl_3$)].




Scheme 3. Synthesis of (+)-coccinine (**9**): a) $n$BuLi (4 equiv), THF, −78 °C, 2 h, 45 %; b) 37 % aq. $CH_2O$, MeOH, RT, 5 min; 6 N HCl, 80 °C, 12 h, 53 %; c) 1. $Et_2O$, anhydrous HCl, 0 °C, 20 min, concentrate in vacuo; *m*-CPBA, $CH_2Cl_2$, 0 °C; 2. $C_6H_6$, $K_2CO_3$, 80 °C, 1.5 h, 76 % based on **28**; d) 1. $Ms_2O$, pyridine, $CH_2Cl_2$, 0 °C, 1 h; 2. CsOAc, DMF, [18]crown-6, 125 °C, 48 h; 3. $K_2CO_3$, MeOH, RT, 3 h, 52 % based on **29**. *m*-CPBA = *m*-chloroperbenzoic acid.

In our initial synthetic planning, examination of molecular models suggested that two conformations, chairlike **30** and twist-boat-like **32**, had good orbital overlap between the 2-azaallyl anion and the anionophile, leading to the *cis*-fused[21] perhydroindoles **33** and **34**, respectively (Figure 3). The

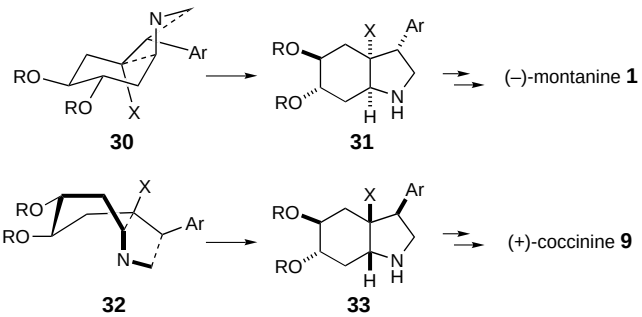



Figure 3. Possible conformations of the 2-azaallyl anion in the cycloaddition.

chairlike conformation **30** appeared to be less congested than **31**. Thus, we predicted that the perhydroindole **31** rather than **33** would result from the cycloaddition.[21] An explanation of this surprising result is under investigation.

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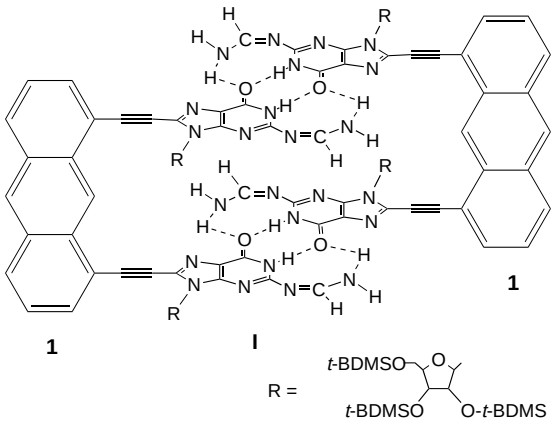
[21] Transition states leading to *trans* ring junctures are not considered based on previous experience.[6b, 9] The alternate chairlike conformation that may lead to **33** is not shown, since it displays severe 1,3-diaxiallike interactions.


## A New Base-Pairing Motif Based on Modified Guanosines**

Jonathan L. Sessler* and Ruizheng Wang

Watson – Crick base pairing involving purine and pyrimidine subunits plays a crucial role in regulating the structures and properties of, for example, duplex DNA and hairpin RNA. Studying synthetic systems with unconventional binding modes could serve to extend the genetic alphabet of DNA and RNA, and produce systems of greater structural diversity, functionality, and catalytic potential.[1] In this context, modified systems derived from guanine are of considerable interest because of their potential antiviral activity and their possibly unique binding ability.[2] However, the number of such systems that have been analyzed in terms of their self-association properties remains limited. One example is 7,9-dimethylguanine, a species that dimerizes in aqueous solution with the formation of three hydrogen bonds.[3] A second example is 5′-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene isoguanosine; this forms a tetramer[4] in organic media that is more stable than the corresponding guanosine tetramer.[5] Here we report the new guanine derivative **1**, which, when constrained within a rigid framework, self-associates in organic solution to form an unprecedented tetrameric guanine-containing array (dimer **I**). What is unique about this system is that it is held together by a pair of four-point hydrogen bonds.[6–8]




The synthesis of **1** (Scheme 1) involves initially a Pd-catalyzed cross-coupling between $N^2$-(*N*,*N*-dimethylformamidine)-protected 8-bromoguanosine (**5**) and organostannyl derivative **4**[9] produced in situ from 1,8-diethynylanthracene (**3**). This sequence gave the bis(guanosine) derivative **6**. Treatment of **6** with methanolic ammonia at room temperature did not give the expected deprotected bis(guanine) derivative **2**, but rather **1**, in which the $NMe_2$ group of **6** is

[*] Prof. J. L. Sessler, R. Wang
Department of Chemisty and Biochemistry
University of Texas
Austin, Texas 78712 (USA)
Fax: (+1) 512-471-7550
E-mail: sessler@mail.utexas.edu

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