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Concise Assembly of the Polycyclic Frameworks Associated with the Hapalindole and Fischerindole Alkaloids

Martin G. Banwell,* Xinghua Ma, Rebecca M. Taylor, and Anthony C. Willis

Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

mgb@rsc.anu.edu.au

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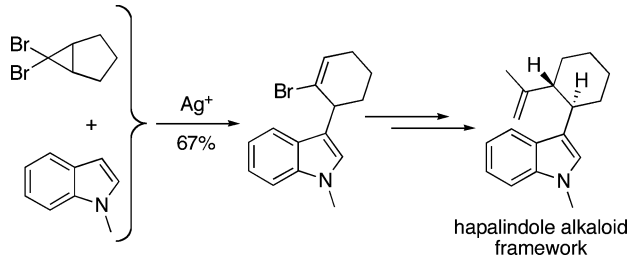
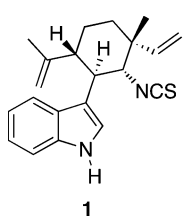
ABSTRACT



Reaction of *N*-methylindole (4) with 6,6-dibromobicyclo[3.1.0]hexane (5) in the presence of silver tetrafluoroborate affords conjugate 7 in 67% yield. This product can be readily elaborated to compounds 12b and 13b which embody the polycyclic frameworks associated with members of the hapalindole and fischerindole classes of alkaloids. The chiral-auxiliary-substituted 6,6-dibromobicyclo[3.1.0]hexanes 21 and 22 react with indole to give adducts likely to be useful in the enantioselective total synthesis of the title alkaloids.

As part of a continuing program[1] to exploit *gem*-dihalocyclopropanes in the synthesis of natural products, we sought to identify carbon-centered (or C) nucleophiles capable of trapping the allylic cations derived from electrocyclic ring-opening of these readily available three-membered-ring compounds. While some seminal work along such lines has been reported by Gassman and co-workers,[2] the range of C-nucleophiles known to participate is limited to simple alkenes and aromatics.[3] Herein, therefore, we report that various indoles also engage, as nucleophiles, in these trapping processes. In addition, we also detail the exploitation of adducts derived from such reactions in the rapid assembly of the polycyclic frameworks associated with the biologically and structurally interesting hapalindole and fischerindole classes of alkaloids,[4] representative examples being (+)-hapalindole Q (**1**)[4b] and (−)-12-*epi*-fischerindole U isothiocyanate (**2**).[4e] These types of natural products, which were



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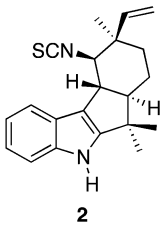

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first isolated by Moore and co-workers and can be found in a variety of organisms, most notably blue-green algae,[4] display anti-bacterial, anti-algal and anti-mycotic activities.[4]

(1) (a) Banwell, M. G.; Gable, R. W.; Peters, S. C.; Phyland, J. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1395. (b) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem.* **2000**, *65*, 4241. (d) Banwell, M. G.; Ebenbeck, W.; Edwards, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 114. (e) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2002. (f) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296. (g) Taylor, R. M. *Aust. J. Chem.* **2003**, *56*, 631. (h) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537. (i) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143. For a review of some of our group's research efforts in this area see: (j) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589.

(2) Gassman, P. G.; Tan, L.; Hoye, T. R. *Tetrahedron Lett.* **1996**, *37*, 439.

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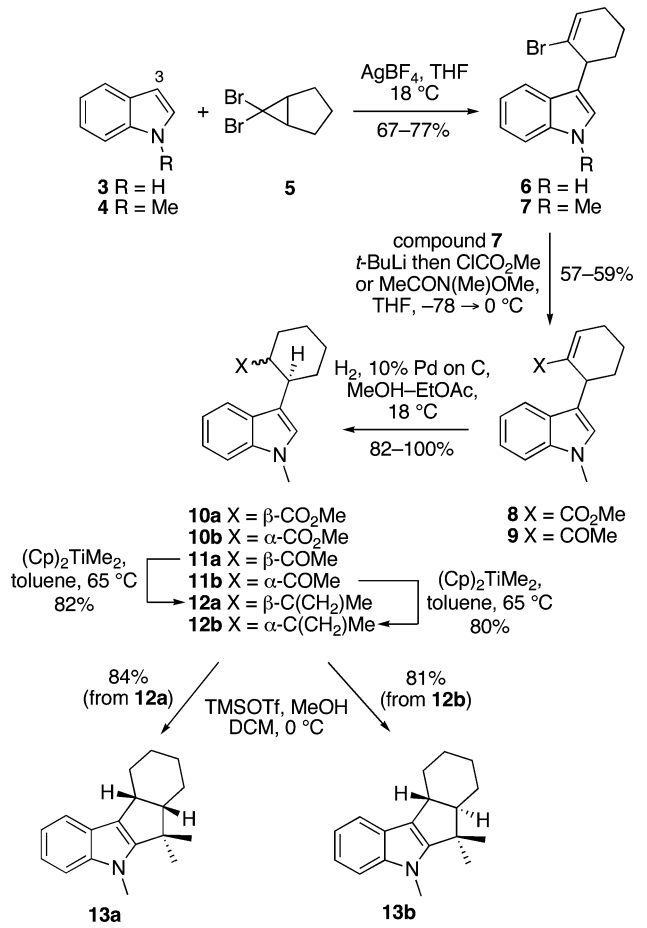
Such properties may be attributable to the compounds' capacities to inhibit RNA polymerase.[5] Accordingly, these alkaloids have stimulated various synthetic studies over the last 15 years or so and total syntheses have been reported by the groups of Natsume, Albizati, Fukuyama, Kerr, and Baran.[6]

Our approach to the title frameworks is shown in Scheme 1 and involved, in the opening stages, an investigation of

Scheme 1



the reaction of the parent indole (**3**) and its *N*-methylated derivative (**4**) with *gem*-dibromocyclopropane **5**, the last compound being readily available through dibromocarbene addition to cyclopentene. In the event, each of indoles **3** and **4** reacted smoothly at 18 °C with equimolar quantities of cyclopropane **5** in the presence of silver tetrafluoroborate to give adducts **6** (77%) and **7** (67%), respectively. These products clearly arise through nucleophilic attack of C-3 of the indoles on the allylic cation derived from electrocyclic ring-opening of the compound **5**. Reaction of cyclohexenyl bromide **7** with 2 molar equiv of *tert*-butyllithium and trapping of the ensuing cyclohexenyllithium with either methyl chloroformate or the Weinreb amide of acetic acid[7] then gave the corresponding α,*β*-unsaturated ester **8**[8] (57%) and methyl ketone **9** (59%), respectively.[9] Subjection of the former product to hydrogenation, at 1 atm, using 10% Pd on C as catalyst gave a ca. 1:1 and chromatographically separable mixture of the *cis*- and *trans*-1,2-disubstituted cyclohexanes **10a** (51%) and **10b** (49%), respectively. Analogous treatment of the acylated alkene **9** afforded a chromatographically separable mixture of compounds **11a** (19%) and **11b** (63%). Methylenation of compound **11a** with the Petasis reagent[10] afforded the alkene **12a** (82%) that upon treatment with TMSOTf underwent cyclization to give the tetracyclic compound **13a**[8] (84%) embodying the *cis*-ring fused variant on the fischerindole framework. Conversion of isomeric ketone **11b** into the corresponding and targeted alkene **12b**, which incorporates key elements of natural products such as hapalidoles C, D, E, F, and Q,[4,6] was accomplished in an efficient manner (80%) by using the Petasis reagent. Furthermore, subjection of the latter compound to what might be regarded as a biomimetic cyclization reaction[6d,g] using TMSOTf afforded the tetracyclic indole **13b**[8] (81%) now embodying the framework associated with the fischerindoles.[11]

The strategy detailed above can also be exploited in the construction of enantiopure indole-substituted cyclohexenes incorporating additional functionality likely to be useful in developing total syntheses of the title alkaloids. The two *gem*-dibromocyclopropanes used in examining this particular aspect of the present studies were prepared by the pathway shown in the early parts of Scheme 2. Thus, oxidation of commercially available 1,6-heptadien-4-ol (diallyl alcohol) to the previously reported[12] diallyl ketone (**14**) was accomplished (90%) with pyridinium chlorochromate (PCC)[13]

(3) Dehmlow, E. V.; Schönefeld, J. *Justus Liebigs Ann. Chem.* **1971**, *744*, 42.

(4) (a) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456. (b) Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036. (c) Moore, R. E.; Yang, X.-Q. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 3773. (d) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257. (e) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.

(5) (a) Doan, N. T.; Rickards, R. W.; Rothschild, J. M.; Smith, G. D. *J. Appl. Phycol.* **2000**, *12*, 409. (b) Doan, N. T.; Stewart, P. R.; Smith, G. D. *FEMS Microbiol. Lett.* **2001**, *196*, 135.

(6) (a) Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351 and references therein. (b) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393. (c) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499. (d) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125. (e) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189. (f) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120. (g) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.

(7) Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851.

(8) The structure of this compound has been confirmed by single-crystal X-ray analysis. (CCDC reference numbers: **8**, 610988; **13a**, 610989; **13b**, 610990.)

(9) Attempts to effect analogous conversions of compound **6** through its reaction with 3.0 molar equiv of *t*-BuLi then either acetyl chloride or methyl chloroformate only resulted in the formation of the *N*-acyl or *N*-carbomethoxy derivatives of the starting material. Similar treatment of the readily derived *N*-Boc derivative of compound **6** gave the same products while its *N*-Ts congener afforded low yields (ca. 30%) of the desired cyclohexenes, viz. the *N*-Ts analogues of compounds **8** and **9**.

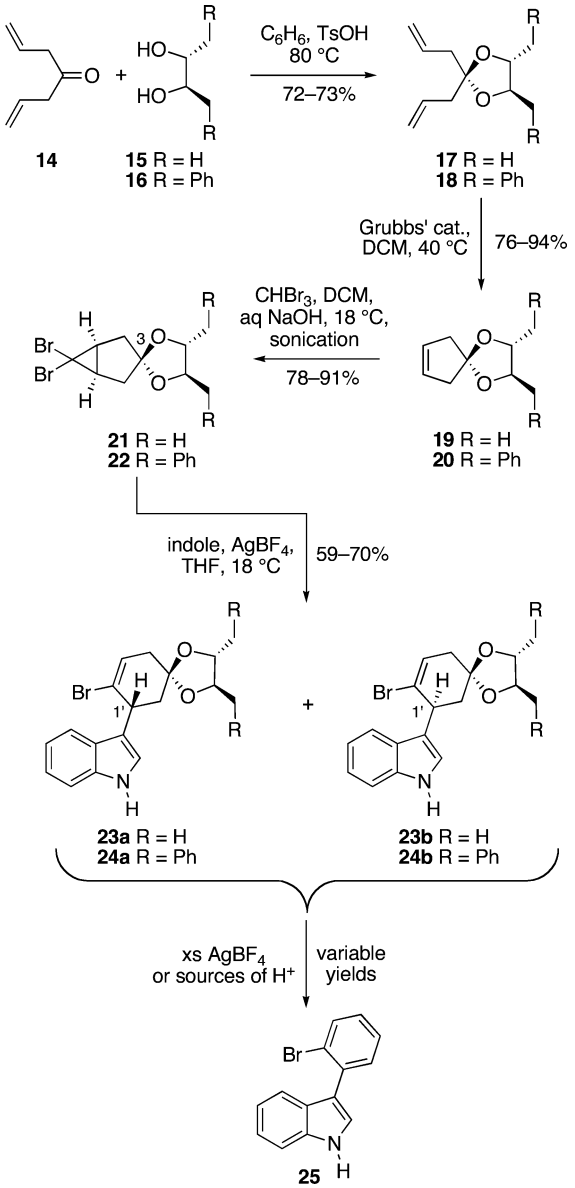
(10) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(11) Methods are available for the demethylation of *N*-methylindoles—see, for example: Nakatsuka, S.; Asano, O.; Goto, T. *Heterocycles* **1986**, *24*, 2791.

(12) Dreyfuss, M. P. *J. Org. Chem.* **1963**, *28*, 3269.

(13) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

Scheme 2



and the latter compound reacted, under conditions specified by Dolbier and Garza,[14] with commercially available (2*R*,3*R*)-butane-2,3-diol (**15**) in the presence of catalytic amounts of *p*-TsOH to give the acetal **17** (73%). An analogous process involving diol **16** afforded the diphenylated system **18** (72%). Subjection of each of these compounds to ring closing metathesis using Grubbs' second-generation catalyst[15] then gave the corresponding cyclopentenes **19** (76%) and **20** (94%). Dibromocarbene addition to the double bonds of the latter compounds, under conditions defined by Xu and Brinker,[16] then afforded the corresponding and targeted ring-fused *gem*-dibromocyclopropanes **21** (91%) and **22** (78%). Reaction of the first of these products, viz. compound **21**, with indole in the presence of silver tetrafluoroborate afforded a 1:1 mixture of adducts **23a** and **23b** (59% combined yield) which could be separated by HPLC techniques. Upon subjecting congener **22**, incorporating the second chiral auxiliary, to the same conditions a ca. 1:1 mixture of compounds **24a** and **24b** (70% combined yield) was obtained. Each of the four adducts **23a**, **23b**, **24a**, and **24b** was prone to aromatization upon prolonged exposure to acidic conditions and thereby affording 3-(*o*-bromophenyl)indole (**25**). Interestingly, the specific rotations of each of the diastereoisomeric compounds **23a** and **23b** proved to be of a similar magnitude but opposite sign. The same is true for congeners **24a** and **24b**. The illustrated stereochemical assignments at C-1′ within each of these adducts must be regarded as tentative at this stage.

The studies described above highlight the ability of indoles to act as C-nucleophiles capable of trapping π-allyl cations derived from electrocyclic ring-opening of ring-fused *gem*-dibromocyclopropanes. The ensuing adducts are obtained in good yield and can be used for the rapid assembly of analogues of the hapalindole and fischerindole classes of alkaloid. Clearly, the diastereoselectivity of these processes is not strongly influenced by the presence of chiral auxiliaries attached to C3 of the 6,6-dibromobicyclo[3.1.0]hexane framework. Work aimed at exploiting the results reported above in various contexts, including the total synthesis of the title alkaloids, is now underway in our laboratories. Details will be reported in due course.

Supporting Information Available: Preparation and characterization of **5**−**14** and **16**−**25**, ^{1}H or ^{13}C NMR spectra for **6**−**13** and **17**−**24**, and X-ray crystallographic data for **8**, **13a**, and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Dolbier, W. R., Jr.; Garza, O. T. *J. Org. Chem.* **1978**, *43*, 3848.
(15) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.
(16) Xu, L.; Brinker, U. H. In *Synthetic Organic Sonochemistry*; Luche J.-L., Ed.; Plenum Press: New York, 1998; pp 344−345.