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Exploitation of Cyclopropane Ring-Cleavage Reactions for the Rapid Assembly of Tetracyclic Frameworks Related to Gibberellins

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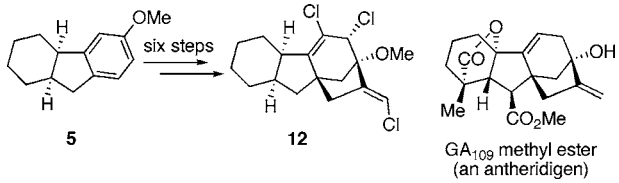
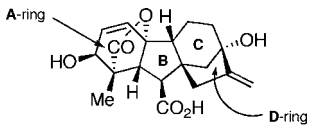
ABSTRACT



The readily available hexahydrofluorene 5 has been elaborated over six steps, including three involving cyclopropane ring-cleavage reactions, into compound 12 which incorporates the carbocyclic framework associated with gibberellins.

The gibberellins (GAs) are a large and seemingly continuously expanding class of structurally complex diterpenoids many members of which exhibit extraordinarily potent plant-growth-regulating properties.[1] Indeed, some such compounds



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exert these types of effects at near femtomolar (10^{-15} M) levels.[1f,2] As a consequence, certain GAs, including gibberellic acid (**1**, aka GA_3), are of considerable agricultural and (therefore) commercial significance.[1e,3] Not surprisingly, then, there have been major activities directed toward the total synthesis of gibberellins[1a−d,f] and spectacular successes have been reported by, inter alia, Mori,[4] Nagata,[5] Corey,[6] Mander,[1b−d,f] De Clercq,[7] Yamada,[8] and Ihara.[9] Notwith-

(1) For comprehensive reviews on the isolation, structural elucidation, biogenesis, chemical properties, and/or synthesis of GAs, see: (a) Fujita, E.; Node, M. *Heterocycles* **1977**, *7*, 709. (b) Mander, L. N. *Acc. Chem. Res.* **1983**, *16*, 48. (c) Mander, L. N. *Nat. Prod. Rep.* **1988**, *5*, 541. (d) Mander, L. N. *Chem. Rev.* **1992**, *92*, 573. (e) MacMillan, J. *Nat. Prod. Rep.* **1997**, *14*, 221. (f) Mander, L. N. *Nat. Prod. Rep.* **2003**, *20*, 49.

(2) (a) Takeno, K.; Yamane, H.; Yamauchi, T.; Takahashi, N.; Furber, M.; Mander, L. N. *Plant Cell Physiol.* **1989**, *30*, 201. (b) Wynne, G. M.; Mander, L. N.; Oyama, N.; Murofushi, N.; Yamane, H. *Phytochemistry* **1998**, *47*, 1177.

(3) The inhibition of GA biosynthesis is also very important. Thus, for example, the semidwarf (sd-1) "green revolution" rice contains a defective gibberellin 20-oxidase gene that retards in vivo production of the relevant GAs - see: (a) Sasaki, A.; Ashikari, M.; Ueguchi-Tanaka, M.; Itoh, H.; Nishimura, A.; Swapan, D.; Ishiyama, K.; Saito, T.; Kobayashi, M.; Khush, G. S.; Kitano, H.; Matsuoka, M. *Nature* **2002**, *416*, 701. (b) Spielmeyer, W.; Ellis, M. H.; Chandler, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 9043.

(4) (a) Mori, K.; Shiozaki, M.; Itaya, N.; Matsui, M.; Sumiki, Y. *Tetrahedron* **1969**, *25*, 1293. (b) Mori, K.; Takemoto, I.; Matsui, M. *Tetrahedron* **1976**, *32*, 1497 and references cited therein.

(5) Nagata, W.; Wakabayashi, T.; Narisada, M.; Hayase, Y.; Kamata, S. *J. Am. Chem. Soc.* **1971**, *93*, 5740.

(6) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034. (c) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129. (d) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611 and references cited therein.

(7) Grootaert, W. M.; De Clercq, P. J. *Tetrahedron Lett.* **1986**, *27*, 1731.

(8) Nagaoka, H.; Shimano, M.; Yamada, Y. *Tetrahedron Lett.* **1989**, *30*, 971.

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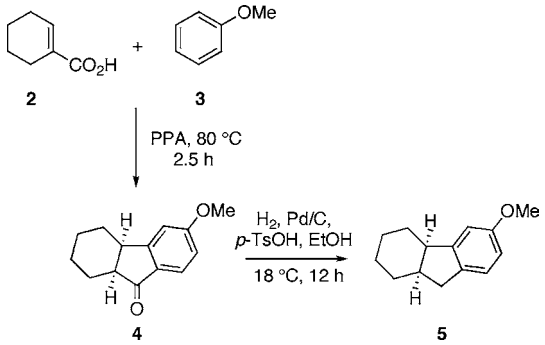
standing the remarkable effort involved, the lengthy nature of the reaction sequences required to complete such work has meant that essentially all research concerned with exploring structure−activity relationships within the class has relied on carrying out chemical modifications of GA_3 which is readily accessible in tonne quantities through fermentation processes.[1b−f] Accordingly, biological studies on these diterpenoids could benefit significantly from the development of simple protocols for the assembly of the gibberellin and related scaffolds, especially ones that possess novel functionality and/or frameworks not likely to be readily accessible through manipulation of GA_3. Such objectives would seem all the more important given the recent identification of the first gibberellin receptor, GID1,[10] and the accompanying development of a proposed mechanism for GA signaling. As a consequence, there now appear to be good prospects for establishing a complete understanding of the molecular basis of action of the GAs and, therefore, an attendant capacity to engage in the rational design of synthetic plant-growth-regulating substances. On this basis, we describe herein a novel and especially concise reaction sequence that enables the rapid assembly of tetracyclic frameworks related to the gibberellins. The key features of the present work are the exploitation of two cyclopropanation and three successive cyclopropane ring-cleavage steps in the elaboration of the methoxy-substituted aromatic ring associated with the hexahydrofluorene **5** into the bicyclo[3.2.1]-octane substructure corresponding to the C- and D-rings of GAs.[11]

The synthesis of the previously unreported cis-ring fused fluorene derivative **5** was readily achieved using the two-step reaction sequence shown in Scheme 1. This starts with the commercially available compounds **2** and **3** and engages them in a PPA-mediated Friedel−Crafts acylation/Nazarov-type cyclization sequence so generating the known fluoren-9-one **4**[12] in 65% yield. Subjection of the last compound to a one-pot hydrogenation/hydrogenolysis sequence, using dihydrogen in the presence of Pd on C and *p*-toluenesulfonic acid, afforded compound **5** in 94% yield.

Scheme 1



The route employed for the purposes of elaborating compound **5** into the title frameworks is shown in Scheme 2 and commences with a Birch reduction step that leads to the corresponding dihydro-derivative **6** (91%). Reaction of this diene with excess dichlorocarbene generated from chloroform under phase-transfer conditions[13] afforded a chromatographically separable mixture of the isomeric compounds **7**[14] (27%) and **8**[14] (45%). The former product most likely arises from dichlorocarbene addition to the slightly less congested α-face of the methoxy-substituted and, therefore, more nucleophilic double bond within substrate **6**. The steric congestion at both faces of the double bond within the resulting monoadduct inhibits addition of a second equivalent of dichlorocarbene such that a C−H insertion process occurs in preference thus affording the dichloromethylated product **7**. In contrast, when dichlorocarbene adds to the *β*-face of the methoxy-substituted double bond within substrate **6** the α-face of the remaining alkene remains accessible to a second equivalent of this divalent species and so allowing formation of the desired bis-adduct **8**. Treatment of compound **8** with potassium *tert*-butoxide in THF at 0 °C resulted in elimination of the elements of HCl and the efficient formation (96%) of the cyclopropane ring-cleavage product **9** now incorporating a chlorinated double bond that will become the exocyclic alkene attached to the D-ring of the target GA framework. While the pathway followed during the conversion **8** → **9** remains to be established, other work conducted in these laboratories has demonstrated that the process can be applied within a variety of frameworks.[15] Heating of compound **9** in 2,6-lutidine for 4.5 h results in a smooth vinylcyclopropane to cyclopentene rearrangement[16] and the formation of the annulated and crystalline norbornene **10**[14] in 89% yield. Compound **10** represents an interesting acquisition because it incorporates a hitherto unreported C-norGA framework and might, therefore, represent a useful scaffold for the development of GA agonists and/or inhibitors of GA biosynthesis. Furthermore, since it is known that the

(9) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. *J. Am. Chem. Soc.* **2000**, *122*, 9036.

(10) Ueguchi-Tanaka, M.; Ashikari, M.; Nakajima, M.; Itoh, H.; Katoh, E.; Kobayashi, M.; Chow, T.-y.; Hsing, Y.-i. C.; Kitano, H.; Yamaguchi, I.; Matsuoka, M. *Nature* **2005**, *437*, 693.

(11) This work was undertaken as part of a program within our group to exploit *gem*-dihalogenocyclopropanes as building blocks for chemical synthesis. For representative publications, see: (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. (j) Foot, J. S.; Phillis, A. T.; Sharp, P. P.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2006**, *47*, 6817. (k) Banwell, M. G.; Vogt, F.; Wu, A. W. *Aust. J. Chem.* **2006**, *59*, 415. For a review of certain aspects of our work in this area, see: (l) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589.

(12) Ramana, M. M. V.; Potnis, P. V. *Synth. Commun.* **1995**, *25*, 1751.

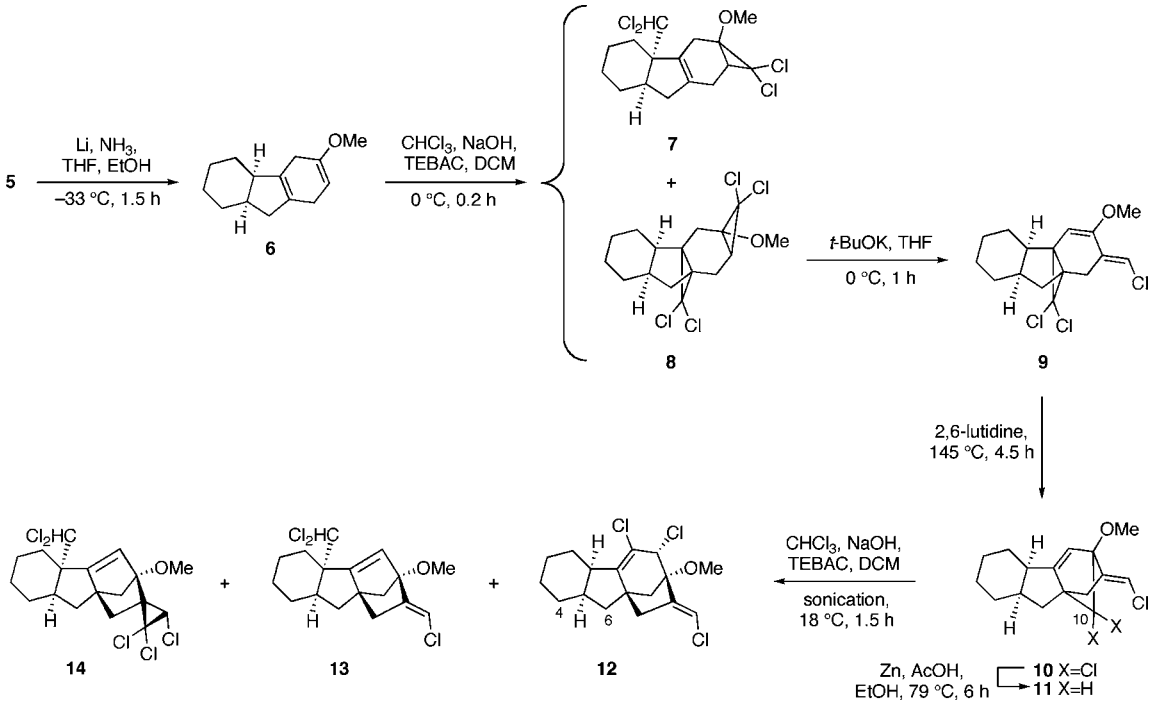
(13) Mąkosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659.

(14) The structure of this compound has been established by single-crystal X-ray analysis. Details are provided in the Supporting Information.

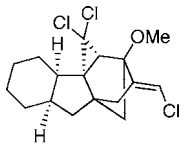
(15) (a) Banwell, M. G.; Gable, R. W.; Halton, B.; Phyland, J. R. *Aust. J. Chem.* **1994**, *47*, 1879. (b) Banwell, M. G.; Phillis, A. T. Unpublished observations.

(16) For a comprehensive review of this type of process see: Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

Scheme 2



gem-dihalocyclopropanes derived from dihalocarbene addition to norbornenes {bicyclo[2.2.1]heptenes} generally engage in spontaneous electrocyclic ring-opening to the corresponding bicyclo[3.2.1]octane,[17] it was thought that dihalocarbene addition to compound **10** might provide a means for its homologation to the GA framework proper. In the event, all efforts to add dichlorocarbene to compound **10** or the corresponding C10-mono-chlorinated derivatives failed. As a result compound **10** was treated with zinc in ethanol in the presence of traces of acetic acid thus forming the doubly dechlorinated compound **11** in 88% yield. The latter compound proved reactive toward dichlorocarbene generated under phase transfer conditions with accompanying ultrasonication[18] and the products **12**[14] (27%), **13** (25%), and **14**[14] (19%) so-formed were readily separated from one another by flash chromatographic methods. The structures of the first and third of these products were confirmed by single-crystal X-ray analysis. Compound **12**, which embodies the tetracyclic GA framework, undoubtedly arises by the anticipated pathway, namely addition of dichlorocarbene to the norbornenyl framework within substrate **11** and so forming the cyclopropane **15** which does not survive but immediately undergoes ring-expansion to form the corresponding bicyclo[3.2.1]octane (viz. **12**). The α-orientation of the allylic chlorine within this last compound reflects the *exo*-face selectivity associated with the carbene addition reaction leading to the intermediate adduct **15**. The dichloromethylated product **13** clearly arises from dichlorocarbene insertion into the allylic C−H bond within substrate **11** and this event then precludes, through steric effects, addition of the same carbene to the norbornenyl double bond. Rather, such addition takes place at the *exo*-cyclic and chlorinated alkene, thus forming the third reaction product, namely compound **14**.



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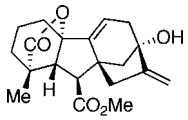
The acquisition of compound **12** as described above represents a six-step method for the assembly of the tetracyclic framework associated with GAs. Furthermore, comparison of the structure of product **12** with that of GA_{109} methyl ester (**16**), a gibberellin-like antheridigen from gametophytes of the fern *Lygodium circinnatum*,[2a] reveals that the synthetic material incorporates functionality highly relevant to the assembly of certain biologically active GA-type natural products. Accordingly, we are now adapting the abovementioned protocols so as to introduce relevant functionalities into the A- and B-rings within these tetracyclic frameworks. In particular, we anticipate incorporating a carbonyl group at C4 and a carboxy unit at C6. The former group would provide the means for inverting stereochemistry at C5, and thus establishing the required *trans*-fusion of the A- and B-rings, as well as a platform for introducing the methyl and carboxy residues at C4. It is also worth noting

(17) See, for example: (a) Jefford, C. W.; Mahajan, S.; Waslyn, J.; Waegell, B. *J. Am. Chem. Soc.* **1965**, *87*, 2183. (b) Sasaki, T.; Eguchi, S.; Kiriyama, T. *J. Org. Chem.* **1973**, *38*, 2230. (c) Kraus, W.; Klein, G.; Sadlo, H.; Rothenwöhrer, W. *Synthesis* **1972**, 485.

(18) Xu, L.; Brinker, U. H. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum Press: New York, 1998; pp 344−345.

that compound **13** embodies a C-norGA framework bearing an angular (and functionalized) methyl group at the junction between the A- and B-rings and thus representing a lower homologue of the so-called C_{20} GAs.



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Work directed toward exploiting the abovementioned observations for the purposes of preparing biologically active analogues of GAs as well as the natural products themselves are now underway in our laboratories. Results will be reported in due course.

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Supporting Information Available: Preparation and characterization of compounds **4**−**14** and ^{1}H and ^{13}C NMR spectra of compounds **4**−**14** together with the ORTEP and certain other material derived from the single-crystal X-ray analyses for **7**, **8**, **10**, **12**, and **14** (CCDC nos. 615227−615231, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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