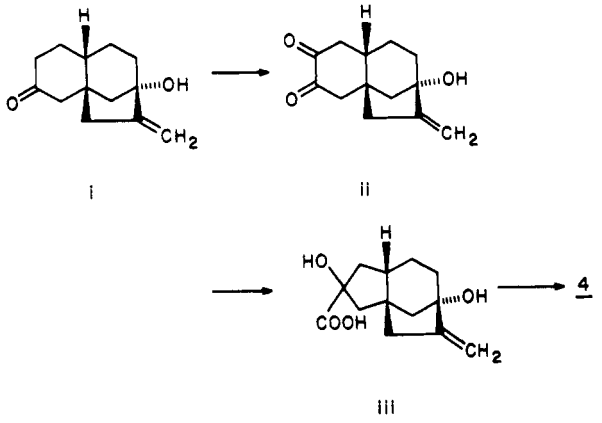
(3) The complete X-ray structure of our tricyclic ketone **4** has been in the literature since 1977,[12] and an outline of one of our more recent syntheses has been available (Taber, D. A. Diss. *Abstr.* **1975,** *35B,* 4399–4400. See also Danheiser, R. L. Ph.D. Thesis, Harvard, 1978). We were therefore surprised that the authors of a very recent communication outlining a synthesis of **23** and other derivatives of **4** (Corey, E. J.; Gorzynski Smith, J. *J. Am. Chem. Soc.* **1979,** *101,* 1038–1039) appeared unaware of our much earlier (and considerably shorter) synthesis.

(4) Stork, G.; Gardner, J. O.; Boeckman, R. K., Parker, K. A. *J. Am. Chem. Soc.* **1973,** *95,* 2014–2017.

(5) The starting material **7** for the cyclization was made from 4-allylcyclohexenone (cf. ref 9) by (1) conjugate addition of cyanide (diethylaluminum cyanide) and dioxolane formation; (2) transformation of the allyl chain into the required α-bromodioxolane by sequential formation of the bromohydrin (*N*-bromosuccinimide, dimethyl sulfoxide), the bromo ketone (chromic acid–acetone), and the bromo diketal. The overall yield from cyclohexane-1,3-dione to **7** was ~20%. It is a pleasure to acknowledge the important contributions of R. L. Danheiser to this particular sequence.

(6) Early and significant contributions to the synthesis of the acetylenic decalindione **15** were made by Dr. J. O. Gardner in this laboratory. This decalindione was our original intermediate to the tricyclic hydrindan **4.** This transformation was initiated by reductive cyclization (cf. **5** → **23**) to the tricyclic decalin derivative i. This was converted into the required hydrindan system by (a) oxidation (O_2, *tert*-butoxide) to the diketone ii; (b) benzilic rearrangement (2:3 20% KOH–propanol, reflux 24 h) to iii; (c) lithium



aluminum hydride reduction of the corresponding methyl ester; and, finally, (d) periodate cleavage to **4.**

(7) Stork, G.; Brizzolara, A., Jr; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963,** *85,* 207–222.

(8) Jacobson, R. M.; Raths, R. A.; McDonald, J. H., III *J. Org. Chem.* **1977,** *42,* 2545–2549.

(9) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973,** *38,* 1775–1776.

(10) Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978,** 2445–2448.

(11) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973,** 957–960.

(12) Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Commun.* **1977,** *6,* 689–693.

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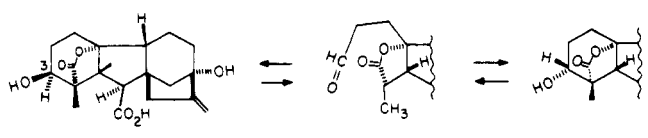
An Unusually Simple Construction of Ring A of Gibberellic Acid

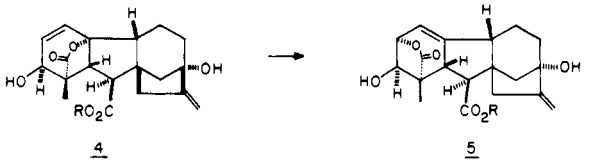
Sir:

It has been suggested[1] that the observed transformation[2] of dihydrogibberellic acid (**1**) into its (more stable) epimer **2** implies retroaldolization to the lactone aldehyde **3**. Its subsequent (reversible) reclosure would then result in the **1** → **2** equilibration.



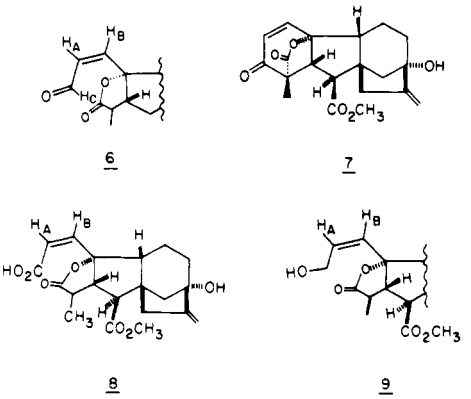
The implication that the dihydrogibberellic acid system might thus be synthesized via the open aldehyde **3** has, in fact, been the basis of some interesting model studies.[3]

The possibility of constructing the A ring area of gibberellic acid (**4**, R = H) *itself* (as opposed to much less strained models)[3] by such a process derives no support from the extensive chemistry of gibberellic acid. In contrast to its much more stable dihydro analogue **1**, gibberellic acid is isomerized, even with 0.01 N NaOH solution at room temperature, to isogibberellic acid[4] (cf. **4** → **5**).



The above result does not imply, however, that there might not be a *kinetic* path that would convert the open aldehyde **6** into gibberellic acid, a transformation which would simplify the problem of total synthesis to such an extent that it appeared worth trying, in spite of the poor prognosis.

The open aldehyde **6** was obtained from the well-known unsaturated ketone **7**,[5] starting with its cleavage (0.05 M



NaOH, 5 min at room temperature) to the unsaturated acid **8**:[6] mp 149–151 °C; 85% yield; NMR δ 5.76 (H_A, d, J = 13 Hz), 6.03 (H_B, d, J = 13 Hz).[7]

The acid was transformed into the desired aldehyde **6** by a three-step sequence: formation of the mixed anhydride (methyl chloroformate, triethylamine, THF, 15 min, room temperature; 90% yield); reduction (sodium borohydride, THF, 0 °C, 30 min) to the allylic alcohol **9** (mp 145–146 °C; 80% yield; NMR δ 5.42 (H_B, d, J = 12 Hz), 5.75 (H_A, dd, J = 5, 12 Hz)); oxidation (MnO_2 in methylene chloride, 12 h at room temperature) to the desired cis unsaturated aldehyde **6** (mp 122–123 °C; 77% yield; NMR δ 6.02 (H_A, dd, J = 7, 13 Hz), 6.43 (H_B, d, J = 13 Hz), 10.32 (H_C, d, J = 7 Hz)).

After a number of attempts to effect base-catalyzed closure of **6**, it was eventually found that catalytic (0.3 equiv, 0.01 M) sodium ethoxide in ethanol (5 min, 0 °C) led, with considerable stereospecificity, to methyl gibberellate. The latter predominated over its C_3 epimer[5b,8] (total isolated yield, 70%) by ~3:1.

Methyl gibberellate (**4**, R = CH_3), identical (mixture melting pointing, spectra) with the natural substance, readily crystallized from the mixture. Alternatively, the mixture could be easily oxidized to the unsaturated ketone **7** in ~70% overall yield from the aldehyde **6**, with MnO_2[9] in methylene chloride.[10]

It may be that the remarkable effect of the change from hydroxide in water to ethoxide in ethanol in suppressing the isogibberellic acid rearrangement is due to the fact that, in spite of appearances, the entity which undergoes rearrangement is actually the hydroxy acid salt (from lactone opening). It also

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may be that a major contribution to the solvolysis of the hydroxy intermediate comes from the higher dielectric constant of the aqueous medium.

Regardless of such mechanistic details, the easy and stereoselective closure of the open aldehydolactone **6** leads to a considerable conceptual simplification in the construction of gibberellic acid.[12]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References and Notes

(1) Stork, G., Newman, H. *J. Am. Chem. Soc.* **1959,** *81,* 5518–5519. See also J. W. Cornforth as quoted by Cross, B. E., *Chem. Ind. (London)* **1959,** 183–185.
(2) Cross, B. E.; Grove, J. F.; MacMillan, J.; Mulholland, T. P. C.; Sheppard, N. *Proc. Chem. Soc.* **1958,** 221–222.
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(4) Cross, B. E.; Grove, J. F.; Morrison, A. *J. Chem. Soc.* **1961,** 2498–2515.
(5) (a) Cross, B. E. *J. Chem. Soc.* **1960,** 3022–3038. (b) Voigt, B.; Adam, G.; Kobrina, N. S.; Serebryakov, E. P. *Z. Chem.* **1977,** *17,* 372–374.
(6) All crystalline compounds were recrystallized from ethyl acetate–hexane and gave ^{1}H NMR data, as well as infrared and mass spectral data, in agreement with those of the assigned structures.
(7) R_F values from thin layer chromatography (silica gel with 3:1 ethyl acetate–hexane) were 0.20, 0.64, 0.35, and 0.50, respectively, for **8**, its mixed anhydride, **9**, and **6**. We believe that the unsaturated acid **8** and the unsaturated aldehyde **6** have a cis double bond, in spite of the rather large coupling constant for the hydrogens labeled H_A and H_B. This is based on the observations (a) that the isomeric unsaturated ester from elimination of the sulfoxide corresponding to the thiophenol adduct of the ester of **8** showed a 16-Hz coupling constant for the hydrogens in question; (b) that the same coupling constant was observed for the unsaturated aldehyde obtained from the alcohol **9** by oxidation with the chromic acid–pyridine complex rather than with manganese dioxide. The cis aldehyde **6** showed the resonance of the aldehyde hydrogen at δ 10.3 while the chromic acid isomer had it at 9.6. The coupling constant of the doublet for that hydrogen was 7 Hz in both cases.
(8) The R_F[7] for methyl gibberellate was 0.51 and for the 3 epimer, 0.47.
(9) Goldman, I. M. *J. Org. Chem.* **1969,** *34,* 1979–1981. This manganese dioxide oxidizes 3-epigibberellic ester, as well as the natural substance in high yield. Compare ref 5b.
(10) Another sequence, applicable to either methyl gibberellate, its C_3 epimer, or a mixture of the two, was carried out: This involves conversion into the 1-bromide (cf. Corey, E. J.; Brennan, T. M.; Carney, R. L. *J. Am. Chem. Soc.* **1971,** *93,* 7316–7317) which gave the acetate of methyl gibberellate with tetrabutylammonium acetate (acetone, 3-h reflux) by an access-controlled S_N2'-type reaction.[11] Free methyl gibberellate (**4**, R = CH_3) was obtained by hydrolysis with sodium bicarbonate in methanol–water (6 h at room temperature).
(11) Stork, G.; Clarke, F. H. *J. Am. Chem. Soc.* **1956,** *78,* 4619–4624. Ganem, B.; Ikota, N. *Ibid.* **1978,** *100,* 351–352.
(12) A successful synthesis of gibberellic acid, based on a different approach, has been reported recently: Corey, E. J., Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. E.; Siret, P.; Grass, J. L. *J. Am. Chem. Soc.* **1978,** *100,* 8034–8036.

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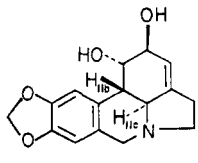
A Simple, Stereospecific Synthesis of the Skeleton of the Lycorine Alkaloids

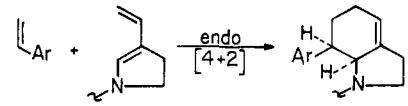
Sir:

We report here a particularly direct route to the galanthan (α-lycorane) system which forms the basic skeleton of lycorine (**1**), the most prevalent of the Amaryllidaceae alkaloids.[1,2]



1

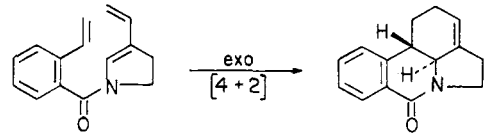
The position of the double bond in lycorine immediately suggests a construction based on a [4 + 2] cycloaddition such as a → b, but the normal endo course of such a cycloaddition would lead to the incorrect cis relationship of the hydrogen at



a b

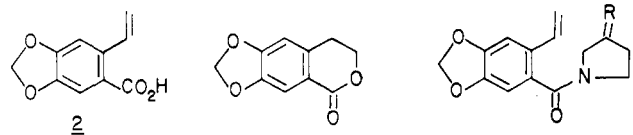
C_{11b} and C_{11c}, a problem which had been encountered previously in intramolecular approaches to **1** from this laboratory.[3]

The situation is entirely changed, however, if a connection between the A and B fragments is established via an amide link, thus making the cycloaddition intramolecular.[4] In such a case, the constraints imposed by the planarity of the amide system are such that only the exo transition state may reasonably be expected (cf. c → d). We describe here the realization of such a scheme.



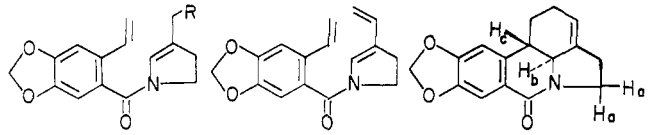
c d

The requisite acid **2**, mp 160–163 °C,[5] readily prepared in 90–95% yield from lactone **3**[7] (addition of **3** and 1.2 equiv of HMPA to 1.2 equiv of $LiN(SiMe_3)_2$ in THF at −78 °C) could be efficiently coupled with 3-pyrrolidinol[8] (1 equiv of **2**, 1.2 equiv of Ph_3P and 5 equiv of CCl_4 in MeCN,[9] 2 h; then, after cooling to 0 °C, treatment with 2 equiv of 3-pyrrolidinol, 0–25 °C, 1 h; 93%) to yield **4a.** Oxidation of **4a** (addition of 4 equiv



2 **3** **4a** R=H, OH
4b R=O

of pyridine–SO_3 complex in Me_2SO[10] and 10 equiv of triethylamine in Me_2SO, followed by quenching after 15 min with ~20 equiv of acetic acid) afforded (79% yield) the keto amide **4b,** which was further elaborated to **5a** either (57% yield) by Emmons–Horner reaction (1.2 equiv each of $(EtO)_2P(O)CH_2CO_2CH_3$ and NaH in glyme, 0 °C, 3 h; then quenched with 2 equiv of acetic acid), which led directly to the thermodynamic β,γ-unsaturated ester, or (60% yield) by Wittig olefination, followed by equilibration (3 equiv of $Ph_3P{=}CHCO_2CH_3$ in methylene chloride, 36 h, followed, after chromatography, by DBU in THF, 18 h). Amide **5a** was



5a R=CO_2CH_3 **6** **7**
5b R=CH_2Se

transformed further by reduction (5.7 equiv of $LiBH_4$, THF, 22 h) and then selenation (1.2 equiv each of *o*-nitrophenyl selenocyanate and Bu_3P[11] in methylene chloride, 5 min) of the

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