conformers. When this conformer was excited and its fluorescence spectrum examined, a broad, red-shifted band was found, while excitation of other conformers resulted in sharp, structured fluorescence.[11] In tryptophan derivatives, the existence of a single conformer showing broad, red-shifted fluorescence and having an extended low-frequency progression in its excitation spectrum was found to correlate with the ability of the molecule to form a zwitterion by proton transfer from the carboxylic acid to the amine group. If such reasoning can be applied to the Trp-Gly dipeptide, one would predict that the conformer with the low-frequency vibrational progression should also show a red-shifted fluorescence spectrum. In Trp-Gly, however, zwitterion formation must involve proton transfer from the glycine to the tryptophan residue since the tryptophan carboxylic acid group is used to form the peptide bond.

Laser desorption has been used in mass spectroscopy to volatilize much larger molecules than the peptides reported here, and it may also provide a general technique for obtaining supersonic molecular beam spectra of such molecules. Although not dramatically larger than Trp-Gly, the tripeptide Trp-Gly-Gly has also been studied in a supersonic molecular beam. Its spectrum, obtained by monitoring the parent ion signal at mass 318, contains an intense, unresolved band that is much narrower than and red-shifted approximately 100 cm^{-1} from the broad Trp-Gly band. A low-frequency progression in a 26-cm^{-1} vibration is also seen approximately 260 cm^{-1} to the red of the main band. As with the dipeptides, the interpretation of the Trp-Gly-Gly spectrum will certainly require the existence of multiple conformers.

Acknowledgment. This work has been supported by the National Science Foundation under NSF CHE-8311971.

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Intramolecular Photocycloaddition. Cyclobutane Fragmentation: Total Synthesis of (±)-Laurenene

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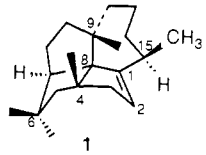
Laurenene (**1**), nature's only known existing fenestrane, was isolated by Corbett and co-workers in 1979 from *Dacrydium cupressinum*. Its unique structure was elucidated by a combi-



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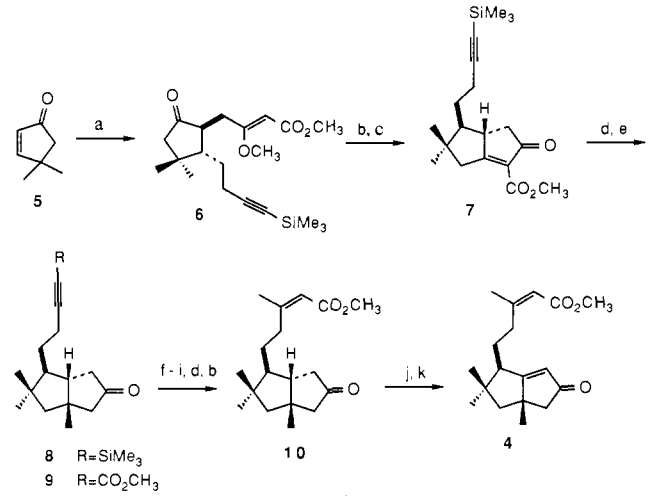
nation of chemical and spectroscopic methods and further confirmed by X-ray crystallography on a brominated derivative.[2] It is a member of the class of angularly fused triquinanes which have recently stimulated much synthetic activity.[3] Laurenene itself, although the subject of much synthetic effort,[4] has not previously yielded to total synthesis. We report here the first total synthesis of this unusual molecule.[4c]

Several salient features of the laurenene system must be considered in any synthetic approach to this molecule: (1) the tetracyclic skeleton of three five-membered rings and one seven-membered ring attached to a central quaternary carbon atom, (2) the stereochemistry of the C-15 secondary methyl, (3) the regiochemistry of the C-1,2 double bond, and most critically (4) the three contiguous quaternary centers at C-4,8,9 which create a severely sterically crowded region wherein the two methyl groups at C-4 and C-9 point directly at one another. Retrosynthetically, it was anticipated that **1** could be obtained from unsaturated ketone **2**. Ketone **2** could be derived from cyclobutane **3** through reductive cleavage of the cyclobutane and refunctionalization. The cyclobutane **3** might be prepared through a [2 + 2] photocycloaddition[5] of enone **4** since we had previously demonstrated in a model system that the three contiguous quaternary centers could be introduced through an elevated temperature intramolecular photocycloaddition.[6] Enone **4** could be prepared from the readily available 4,4-dimethylcyclopent-2-en-1-one (**5**).[7]

Scheme I[a]



[a] (a) $BrMgCH_2CH_2CCSiMe_3$, $[CuIPBu_3]_4$, THF, −50 °C, 2 h; then HMPA, $ICH_2C(OCH_3)=CHCO_2CH_3$, 25 °C, 1 h; (b) 10% HCl, acetone, 6 h; (c) NaOMe, MeOH, 0 °C, 30 min; (d) Me_2CuLi, Et_2O, −78 °C, 30 min; (e) LiCl, H_2O, DMSO, 140 °C, 15 min; (f) *p*-TsOH, $(CH_2OH)_2$, C_6H_6, 80 °C, 5 h; (g) KF, $Bu_4N^+F^-$, CH_3CN, 80 °C, 2 h; (h) BuLi, THF, CO_2, −78 °C; (i) 10% HCl, then CH_2N_2, Et_2O; (j) $Me_3SiCH_2CO_2Et$, THF, Bu_4NF (catalyst), −78 °C, 1 h; then 25 °C, 1 h; (k) $Pd(OAc)_2$, CH_3CN, *p*-benzoquinone, 6 h.

Thus, our attention was initially focused on the preparation of the keto ester **4**. Copper-catalyzed conjugate addition of the Grignard reagent prepared from 4-bromo-1-(trimethylsilyl)-1-butyne[8] to dimethylcyclopentenone **5** (Scheme I) followed by alkylation of the regiospecifically generated enolate with methyl 4-iodo-3-methoxycrotonate[9] provided the crystalline (mp 46–48 °C) trans substituted cyclopentanone **6**[10] in 60% yield. Hydrolysis of the enol ether of **6** (10% HCl; acetone) followed by base-induced cyclization (NaOMe; MeOH; 0 °C; 15 min)[6] provided the diquinane **7** (mp 65–68 °C). Exposure of **7** to lithium dimethylcopper and subsequent decarbomethoxylation (DMSO, H_2O, LiCl)[11] gave ketone **8**[10] in 71% overall yield from **6**. Conversion of **8** to **9** was readily achieved by protection of the ketone [$(CH_2OH)_2$, *p*-TsOH, C_6H_6, 80 °C], removal of the trimethylsilyl group [KF; $Bu_4N^+F^-$ (catalyst); CH_3CN; 80 °C, 2 h], and carbomethoxylation of the terminal acetylene to produce **9** in 90%

(1) Fellow of the Alfred P. Sloan Foundation, 1986–88.
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(10) All new compounds gave consistent ^1H NMR, IR spectra, and elemental analyses.

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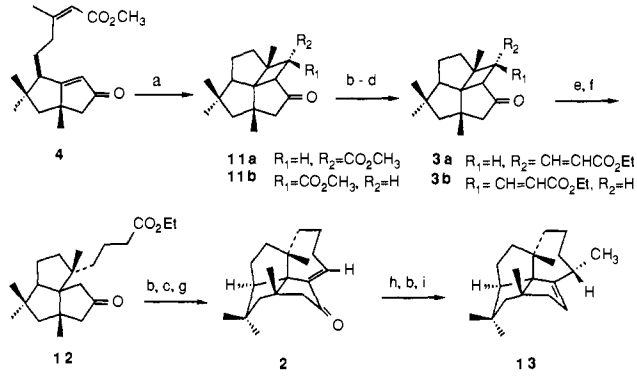
Scheme II[a]



[a] (a) $h\nu$, >350 nm, 110 °C, C_6H_5Cl; (b) $LiAlH_4$, Et_2O, 25 °C; (c) Me_2SO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C; (d) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 40 °C, 1 h; (e) Na, NH_3, Et_2O, −33 °C, 5 min; (f) H_2, Pd/C, EtOH; (g) *p*-TsOH, C_6H_6, 80 °C, 3 h; (h) Me_2CuLi, Et_2O, −78 °C, 30 min; (i) $SOCl_2$, C_5H_5N, 0 °C, 1 h.

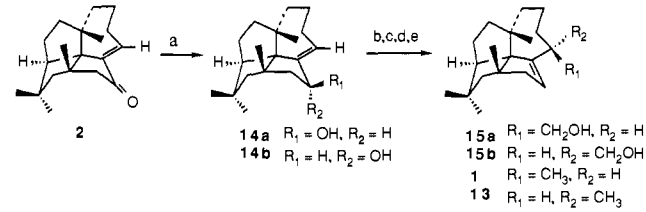
overall yield. Treatment of **9** with lithium dimethylcopper[12] followed by hydrolysis of the ketal (10% HCl; acetone) resulted in a 2:1 mixture of *Z*:*E* isomers of **10** in 89% yield from **9**. Introduction of the double bond to transform **10** to **4** was achieved by regioselective (ca. 9:1) formation of the trimethylsilyl enol ether of **10** [ethyl(trimethylsilyl)acetate; $Bu_4N^+F^-$; THF; −78 °C to 25 °C][13] and subsequent oxidation with palladium acetate and *p*-benzoquinone in acetonitrile[14] to provide **4**[10] in an overall yield of 80% (10% recovered ketone **10**). With a serviceable route to **4** available, the critical photocycloaddition of **4** was carried out in an analogous fashion to earlier model studies.[6] Irradiation of a solution of **4** (Scheme II) in hexane at room temperature resulted in isolation of only starting enone **4** with no evidence of cycloaddition. However, irradiation of a chlorobenzene solution of **4** at 100 °C (uranium filter > 350 nm) produced a 1.5:1 ratio of **11a**:**11b**[10] in 87% yield. **This crucial reaction established the three contiguous quaternary centers required for the sterically congested central portion of laurenene.** The failure to achieve cycloaddition at 25 °C is apparently the result of a severe steric interaction in the transition state for cyclization between the two methyl groups which ultimately reside at carbons 4 and 9 of laurenene.

Isomers **11a** and **11b** could be carried on separately or simultaneously as a mixture to keto ester **12** by a straightforward sequence. Reduction of **11** ($LiAlH_4$, ether), Swern[15] oxidation to the keto aldehyde, and subsequent exposure to carbethoxymethylenetriphenylphosphorane (CH_2Cl_2; 40 °C; 30 min) produced unsaturated esters **3a**,**b** in 89% overall yield from **11**. Reductive cleavage[16] of the cyclobutane of **3a**,**b** by exposure to sodium–ammonia at −33 °C followed by hydrogenation of the resultant β,γ-unsaturated ester (EtOH, Pd/C) yielded 80% of keto ester **12** from **3**.

The remaining cycloheptane ring was closed by reduction–oxidation [$LiAlH_4$, ether; then Swern] of keto ester **12** to generate the analogous keto aldehyde which underwent smooth intramolecular aldolization–dehydration (*p*-TsOH, C_6H_6, 80 °C) to produce enone **2** in 75% overall yield from **12** (12.7% overall from **5**).

Transformation of enone **2** to laurenene **1** in theory required only stereocontrolled addition of lithium dimethylcopper and conversion of the resultant enolate or ketone into the required double bond. Addition of lithium dimethylcopper followed by trapping of the enolate with diethylchlorophosphate gave a single enol phosphate. Unfortunately, attempted reduction of the enol phosphate gave a complicated mixture. When **2** was treated with lithium dimethylcopper followed by lithium aluminum hydride reduction and dehydration with thionyl chloride in pyridine, 15-epilaurenene **13** was the exclusive product. When other attempts to incorporate the secondary methyl in this manner failed, we turned to an alternative approach to rectify the stereochemical problem.

Scheme III[a]



[a] (a) $NaBH_4$, $CeCl_3$, MeOH; (b) KH, Bu_3SnCH_2I, THF; (c) BuLi, hexane, 0 °C; (d) TsCl, pyridine; (e) $LiEt_3BH$, THF.

Reduction of enone **2** (Scheme III) with sodium borohydride–cerium chloride in methanol[17] gave a 1:3 mixture of alcohols **14a**:**14b** in 90% yield. These alcohols were separated by flash chromatography, and the major isomer was treated according to the protocol established by Still[18] (KH, Bu_3SnCH_2I, THF, then BuLi, hexane, 0 °C) to produce 60% of alcohol **15b**. Tosylation of this primary alcohol and reduction with lithium triethylborohydride[19] (70% overall) once again gave only 15-epilaurenene.[20] It would appear that attack at the β-carbon of the enone is sterically more accessible from the α-face due to the position of the methyl at C-9 while attack from the α-face of the carbonyl carbon is *restricted* due to the α-methyl at C-6 resulting in production of the unnatural C-15 isomer in both sequences. However, when the minor alcohol **14a** was exposed to Still's conditions and the resultant alcohol (57% yield) reduced via its tosylate, 72% of (±)-laurenene **1** was produced. This was confirmed by comparison of the ^1H and ^{13}C NMR spectra[21] of synthetic **1** with those of an authentic sample provided by Professor Rex T. Weavers.[22] While the *minor* isomer of the reduction of enone **2** resulted in production of laurenene, higher efficiency can be realized by recycling the major isomer (Jones, acetone; then $NaBH_4$, $CeCl_3$, MeOH).

In summary, the first total synthesis of the structurally unique diterpene (±)-laurenene has been completed. The sequence required 27 steps from 4,4-dimethylcyclopent-2-en-1-one. The key transformation was an elevated temperature intramolecular photochemical cycloaddition which served to establish the crucial three contiguous quaternary carbon centers.

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(20) 15-Epilaurenene: 250 MHz ^1H NMR ($CDCl_3$) δ 0.95, 1.07, 1.11, 1.32 (4 s, 12 H), 1.24 (d, *J* = 6.5 Hz, 3 H), 1.05–2.05 (band, 14 H), 2.55 (dd, *J* = 5 Hz, 11.5 Hz, 1 H), 2.80 (m, 1 H), 5.43 (br t, 1 H); 400 MHz ^{13}C NMR ($CDCl_3$) δ 19.02, 23.10, 24.61, 26.27, 27.12, 29.70, 30.75, 34.91, 36.72, 38.66, 38.97, 39.33, 45.46, 47.39, 49.75, 55.82, 56.68, 60.56, 128.63, 153.89.
(21) Laurenene: 250 MHz ^1H NMR ($CDCl_3$) δ 0.92, 0.97, 1.04, 1.34 (4 s, 12 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.14–1.94 (band, 12 H), 2.00 (ABq, 2 H), 2.36 (m, 1 H), 2.46 (dd, *J* = 9 Hz, 9 Hz, 1 H), 5.37 (br s, 1 H); 400 MHz ^{13}C NMR ($CDCl_3$) δ 20.35, 20.53, 21.95, 24.26, 26.48, 29.22, 29.71, 30.21, 34.61, 36.08, 38.18, 40.81, 41.26, 46.37, 48.75, 54.76, 56.79, 61.50, 121.38, 154.74.
(22) University of Otago, Dunedin, New Zealand.