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THE TOTAL SYNTHESIS OF ALLAMANDIN

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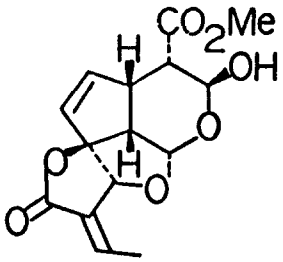
SUMMARY: The first synthesis of (±)-allamandin is accomplished as a result of the successful one step conversion of plumericin.

In 1974 Kupchan and coworkers reported the isolation of several new iridoid lactones from an ethanolic extract of the roots of Allamanda cathartica.[1] Of these compounds, allamandin possessed significant activity in vitro against cells derived from human carcinoma of the nasopharynx (KB). It was assigned structure 1 based upon combustion analysis and ^{1}H-NMR, IR, UV and mass spectral data. Recently, we have described the total synthesis of (±)-plumericin 2,[2] a related iridoid also possessing significant antileukemic activity. We envisioned an acid catalyzed hydration of the C3-C4 olefin of 2 to give what should be the



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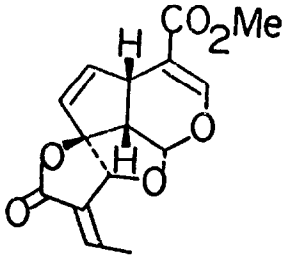

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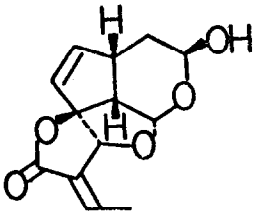

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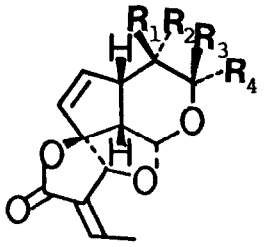
thermodynamically most stable trans-β-hydroxyester as present in allamandin. However, under a variety of mild, acidic conditions (wet silica gel,[3] $AgClO_4$-aqueous CH_3CN,[4] dilute H_3O^+-room temperature, acidic alumina-aqueous THF, concentrated H^+-room temperature) no reaction was observed. We now wish to report the successful conversion of 2->1[5] which completes the total synthesis of allamandin.

A more vigorous set of conditions was sought because of the lack of reactivity exhibited by plumericin. When 2 was refluxed with 0.24 N HCl for 5.5 h, a single product was obtained in ca. 90% yield. This compound proved to be descarbomethoxyallamandin 3[2] by comparison with the ^{1}H-NMR spectrum and the TLC behavior of authentic material. In light of this result, a chemoselective method was sought to allow hydration of the olefin of the vinylogous carbonate of 2 without hydrolysis and subsequent decarboxylation of the ester.

The activation of olefins by cationic rhodium complexes[6] allows the addition of ethanol[6b] or amines[6c] to 1,3-dienes. We had hoped that this affinity might activate the more electron rich C3-C4 olefin of 2 toward addition of water while the ester remained intact. Therefore, a suspension of plumericin in 0.011M aqueous $RhCl_3 \cdot 3H_2O$ containing a small amount of methanol was refluxed for 4 h. Preparative TLC gave three bands, 1) unreacted plumericin (25%), 2) allamandin contaminated with unidentified by-products and 3) a trace of descarbomethoxyallamandin. The middle band was triturated with ether to give pure allamandin 1[7] (16%).

Since $RhCl_3 \cdot 3H_2O$ reacts with water to liberate HCl, the following experiment was performed: plumericin was refluxed with 0.02 N HCl-CH_3CN (3:1) for 4 h giving a mixture of starting material 2, pure allamandin 1 and a substantial amount of 3. Because of the absence of by-products and the higher mass balance in this run, the acid catalyzed hydration was pursued further. Utilizing a higher pH and a less nucleophilic counter ion, a suspension of plumericin in 0.010 N $HClO_4$ was heated to 95-100°C under a N_2 atmosphere for 9 h. Purification by preparative TLC afforded recovered plumericin (31%), allamandin (39%, 55% based upon recovered 2), mp 207-208.5°C, and descarbomethoxyallamandin (6%). The spectral characteristics of 1 were identical to those of an authentic sample of (+)-allamandin.[8]

Structure 1 was assigned to allamandin by Kupchan, et. al. based upon the inspection of Dreiding models and the observed coupling constants $J_{1,9}$, $J_{4,5}$ and $J_{3,4}$.[1] We believe that the C3-C4 stereochemistry is the thermodynamically most stable one, however, depending upon the conformation of the tetrahydropyran ring,



4 R_1=CO_2Me, R_4=OH, R_2=R_3=H

5 R_1=CO_2Me, R_3=OH, R_2=R_4=H

6 R_2=CO_2Me, R_4=OH, R_1=R_3=H

one can argue that compound 4 or even 5 is also a viable structure. Therefore, MM2 calculations[9] were performed on the possible stereoisomers of this system. The relative total energies, E (kcal) are: E(6)=2.53, E(4)=2.34, E(5)=0.05 and E(1)=0.00. Although the calculations do not include hydrogen bonding which is presumably important in this case, they suggest that a simple inspection of a model cannot answer the question of the relative stereochemistry. Structure 1 should be regarded as tentative until the stereochemistry is proven.

Acknowledgements. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We also thank Professor W. Clark Still for the use of his molecular mechanics program.

References and Notes

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4. L.-F. Tietze, private communication.

5. An approach to allamandin has been described: Whitesell, J.K.; Deyo, D. 188th ACS National Meeting, Philadelphia, PA; August 26-31, 1984; Orgn, 47.

6. a) Cramer, R. Accts. Chem. Res., 1968, 1, 186. b) Dewhirst, K.C. J. Org. Chem., 1967, 32, 1297. c) Baker, R.; Halliday, D.E.; Tetrahedron Lett., 1972, 2773.

7. Spectroscopic data: IR ($CHCl_3$) 3360, 1735, 1680, 1440, 1010 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 7.15 (1 H, qd, J=7,1.5 Hz), 6.01 (1 H, dd, J=6,2 Hz), 5.82 (1 H, dd, J=6,2 Hz), 5.67 (1 H, d, J=4.5 Hz), 5.46 (1 H, dd, J=8,3 Hz), 5.14 (1 H, br s), 3.79 (3 H, s), 3.61 (1 H, m), 3.07 (1 H, dd, J = 8, 4.5 Hz), 2.88 (1 H, d, J=2.5 Hz), 2.78 (1 H, dd, J=8, 4.5 Hz), 2.04 (3 H, d, J=7 Hz). m/e 308, 290, 232, 211, 135, 97. Calculated mass for $C_{15}H_{16}O_7$: 308.0891, found: 308.0892.

8. We would like to thank Professor John M. Cassady of Purdue University for the generous gift of (+)-allamandin.

9. W. Clark Still's molecular mechanics program Model version 1.3 was used. The following torsional parameters for atom types (3 2 1 6) were utilized: V_1=0, V_2=0, V_3=0. Note: MM2 approximates conjugated pi-systems; the C11-C12 bond length is ca. 1.35 angstroms.

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