Tetrahedron Letters,Vol.29,No.21,pp 2539-2542,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHETIC APPROACHES TO BREVIANAMIDES A AND B I. PREPARATION OF 4-p-METHOXYBENZYL-5-(1'-CARBOMETHOXY-2'-[1",1"-DIMETHYLALLYL-2',3'DIHYDROINDOLE]METHYLIDENE)-1,2-L-PYROLIDINOPIPERAZINE-3,6-DIONE VIA AN IRELAND ESTER ENOLATE CLAISEN REARRANGEMENT.

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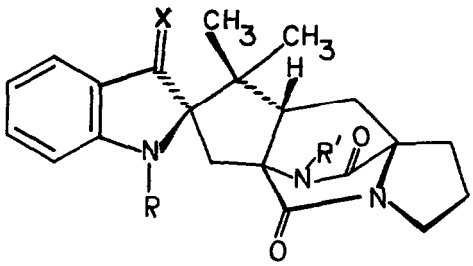
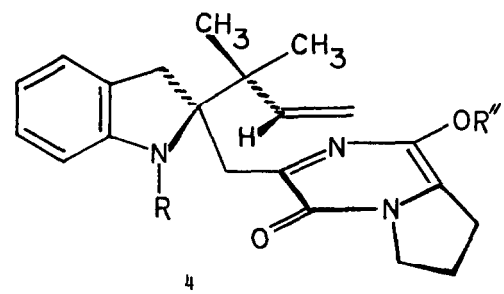
Using an ester enolate Claisen rearrangement to prepare 1-carbomethoxy-2-(1',1'-dimethylallyl)-2,3-dihydroindole-2-carboxylic acid followed by condensation with N-p-methoxybenzyl-glycyl-L-proline anhydride gave the title compound, a key intermediate in a synthetic approach to brevianamides A and B.



1 R = R' = H, X = O

3 X = H_2



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Brevianamides A and B (1, 2) neutral metabolites isolated from the Penicillium brevi-compacum Dierckx mold, contain a more complex spirocyclic fusion of an isoprenyl unit to the 3-oxindole in contrast to structurally simpler brevianamides C and D.[2] This spirocyclic functionality is also found in the toxic metabolite austamide. In their elegant synthesis of austamide, Kishi and Hutchinson elaborated the spirocyclic indoxyl using a stereospecific pinacol-type rearrangement in the latter part of their synthetic scheme.[3] A recent preparation of a tricyclic diketopiperazine portion of 1 and 2 by Williams and Glinka also follows a retrosynthetic scheme in which a rearrangement protocol will be used in the final stages for establishing the spirocyclic junction.[4] In contrast, our synthetic plan to 1 and 2 via 3 and 4 has been proposed to utilize an intramolecular Diels Alder approach for construction of the spirocycle during formation of the tricyclic diketopiperazine.[1] This plan requires that the diketopiperazine moiety be attached to a 2,3-dihydroindole containing the spirocyclic substituents. The synthesis of the key intermediate 4-p-methoxybenzyl-5-(1'-carbomethoxy-2'-[(1",1"-dimethylallyl)-2',3'-dihydroindole]methylidene)-1,2-L-pyrolidinopiperazine-3,6-dione (5), illustrative of this approach, is described.

The synthesis of 5 from methyl indole-2-carboxylate (6)[5] is outlined in Scheme I. Reduction of 6 with magnesium in methanol[6] followed by protection with the N-carbomethoxy group afforded methyl-1-carbomethoxy-2,3-dihydroindole-2-carboxylate (7). The choice of the methylcarbamate protecting group was critical to the steric and electronic requirements of several subsequent reactions including its stability to enolate formation and acid reduction.

Transesterification of 7 to 8 was effected in excellent yield using refluxing 3-methyl-2-buten-1-ol catalyzed by DBU in the presence of 4 Å molecular sieves. The product 8 and all subsequent N-methoxycarbonyl products existed as a mixture of amide rotamers in various proportions depending on the steric congestion caused by groups at C-2. Subjection of 8 to the Ireland ester enolate Claisen rearrangement protocol[7] afforded 1-methoxycarbonyl-2-(1',1'-dimethylallyl)indoline-2-carboxylic acid 9 in 74% yield along with 10% of recovered 8. Acid 9 was converted to its acid chloride and, without isolation,reduced using Vitride[8] followed by Swern oxidation of the resulting alcohol to give 1-methoxycarbonyl-2-(1',1'-dimethylallyl)indoline-2-carboxyaldehyde (10) in 60% overall yield from (9).

The requisite diketopiperazine for condensation with 10 was prepared by cyclizing N-trichloroethoxycarbonyl(Troc)glycyl-L-proline methyl ester (11) with zinc in refluxing methanol followed by nitrogen protection affording p-methoxybenzyl-N-glycyl-L-proline anhydride (12) in 78% yield from 11.

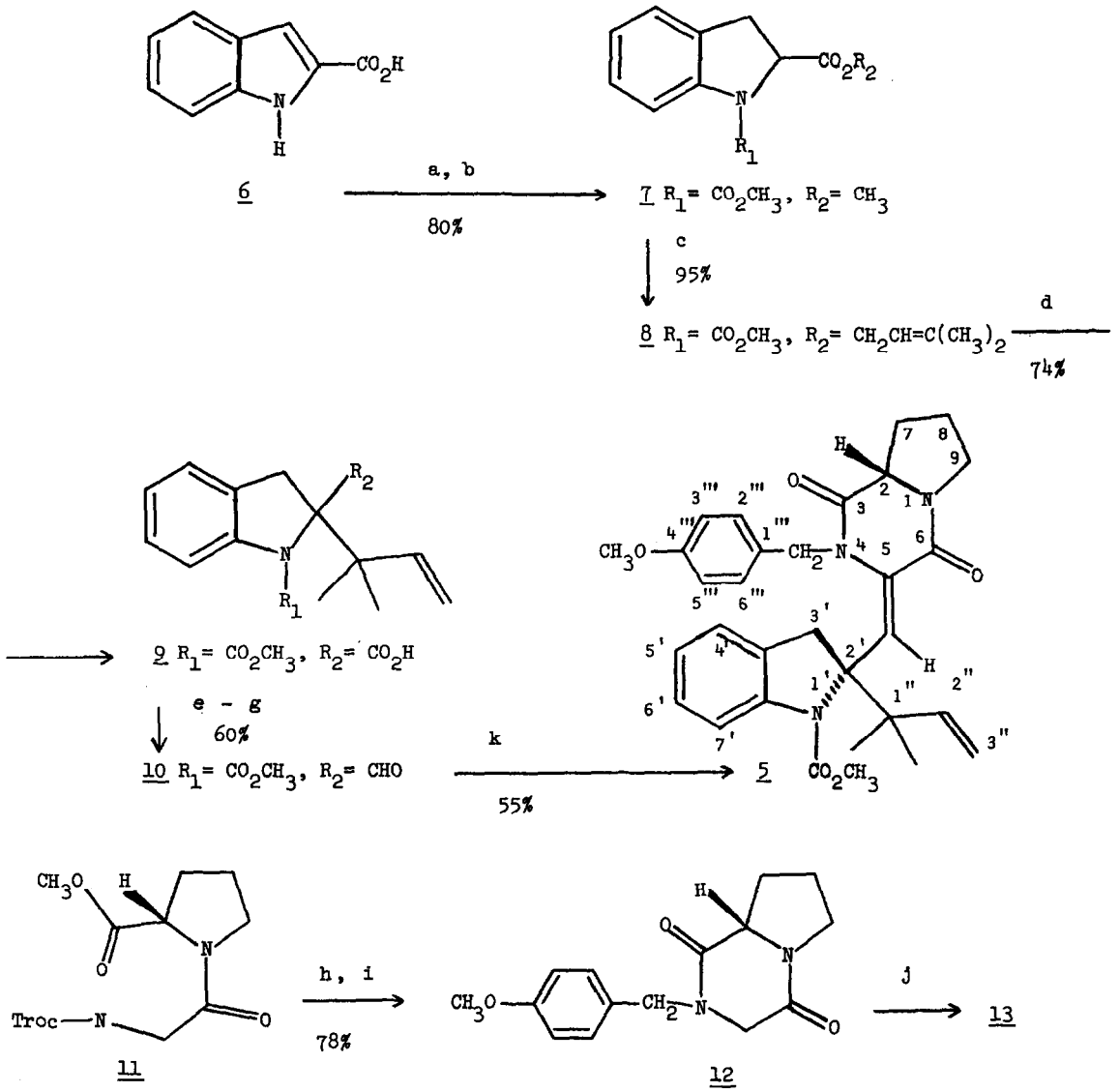
The aldol methodology developed by Nakatsuka and co-workers was applied to the condensation of 12 with 10.[10] Thus, generation of enolate 13 followed by addition of 10 and mesylate elimination afforded 5 in 55% yield after work up and chromatographic purification on silica gel. The Z configuration of 5 was confirmed by the ^1H NMR shift effect of the indoline on the methoxybenzyl CH_2 protons, in which one was shifted upfield and the other downfield. Based on its 500 MHz ^1H NMR and 75.5 Mz ^{13}C NMR spectra, 5 is a mixture of epimers in approximately a 4:1 ratio, suggesting that some kinetic resolution was achieved in the aldol condensation. By examining models, the assignment of the configuration at the spirocyclic chiral center, C-2', is tentatively suggested to be R, based on the preferred conformation of (R)-C-2'-5 in which proximity of the aromatic rings to each other causes H-7' to be shielded and H-3"' and H-5"' to be deshielded more than in the preferred conformation of (S)-C-2'-5. The R configuration at C-2' of 5 compares to that found in Brevianamide A (1). Either configuration at C-2' would make possible an asymmetric synthesis of both 1 and 2 since they are photochemically interconvertable. Unequivocal assignment awaits the X-ray results on a crystalline product.[11]

The results described herein indicate that the Ireland ester enolate Claisen rearrangement can be successfully employed to provide 2-substituted indoline carboxylates which, after reduction to the aldehyde, can be used in a diastereoselective aldol condensation towards an asymmetric approach to brevianamides A and B.

Acknowledgments

Support for this research from the Research Development Association of Southern Illinois University is gratefully acknowledged. The assistance of Steven Elmore, Thomas Lessen, Mark Johnson, Martin Grieme, and Suzanne Steirer is gratefully acknowledged. Nuclear magnetic spectra were provided by the SIUC NMR Facility with assistance from Mitch Sasa and from the Purdue Biomagnetic Resonance Laboratory (NIH RR 01077) with help from Dr. W. M. Westler. Low resolution mass spectra were obtained on a Finnigan 3300 GCMS at Washington University School of Medicine courtesy of Dr. Dennis M. Bier, M.D., and Richard Burger. High resolution mass spectra were obtained from the Southern Illinois mass spectrometry facility from Ken Walsh, sponsored by the Department of Energy.

Scheme I



(a) Mg, CH_3OH; (b) $ClCO_2CH_3$, THF, DMAP, 8h; (c) xs $(CH_3)_2C{=}CHCH_2OH$, cat. DBU, 4A mol sieves, reflux, 0.5h; (d) i. 1.1 eq. LDA, THF, -78°, 0.5h; ii. 2 eq. TMSCl, THF, -78° → rt, 0.5h; iii. THF, reflux, 3.5h; (e) ClCOCOCl, toluene, 0.5h; (f) Vitride, toluene, -40°, 18h; (g) DMSO, ClCOCOCl, Et_3N, 2h; (h) Zn, CH_3OH, reflux; (i) NaH, DMF, p$CH_3OC_6H_4CH_2Cl$; (j) LDA, THF, -78°, -15° 1h; (k) i. 13; ii. CH_3SO_2Cl, -15° → rt, THF; iii. reflux THF, 4h.

NOTES AND REFERENCES

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(Received in USA 1 October 1987)