Tetrahedron Letters Vol.21, pp 4827 - 4830 0040-4039/80/1208-4827$02.00/0

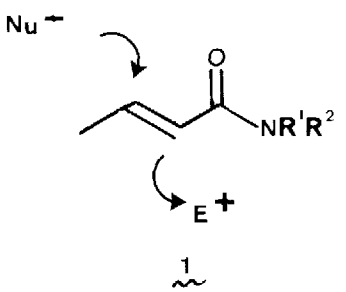
TANDEM CONJUGATE ADDITION-α-ALKYLATION OF UNSATURATED AMIDES. SYNTHESIS OF 1-ARYLTETRALIN LIGNANS

G.B. Mpango and V. Snieckus*

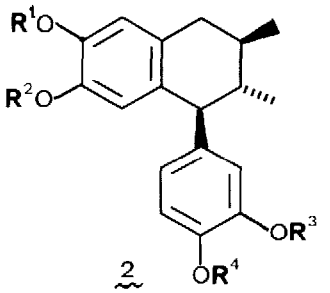
The Guelph-Waterloo Centre for Graduate Work in Chemistry, Waterloo Campus
Department of Chemistry, University of Waterloo, Waterloo, Canada N2L 3G1

Summary: The amide alcohols 5,6, obtained in one step from the sequential reaction of N,N-dimethylcrotonamide with dithiane 3 anion and aryl aldehyde 4, were efficiently converted into the lignans galcatin (2a) and isogalcatin (2b).

In the preceding Letter,[1] we demonstrated that the tandem conjugate addition-α-alkylation of secondary and tertiary crotonamides (1), comprising the formation of two new C-C bonds in one step, is a synthetic method of considerable scope and generality. Herein we describe the application of this strategy to the preparation of the 1-aryltetralin lignans galcatin (2a) and isogalcatin (2b) (Scheme). Although the lignans represent a well-established class of natural products,[2] they have recently attracted quickening synthetic interest[3] as a result of the elucidation of unusual new structures,[2b] the revision of early structural assignments,[4] and the discovery of antileukemic properties in both old (podophyllane)[5] and new (stegane)[6] subgroups.



1



2

a: $R^1 + R^2 = CH_2$, $R^3 = R^4 = Me$
b: $R^1 = R^2 = Me$, $R^3 + R^4 = CH_2$

Sequential treatment of N,N-dimethylcrotonamide with the anion of piperonal dithian (3a) and veratraldehyde (4b) under standard conditions[1] gave a diasterioisomeric mixture of amide alcohols 5a,6a which were separated by column chromatography:[7] 5a(threo): 70%; mp 161-162°C; IR ν 3390, 1610 cm^{-1}; NMR ($CDCl_3$-D_2O) δ 5.03 (1H, d, J=2.6 Hz), 3.87 (1H, d d, J=7.3, 2.1 Hz); 6a(erythro); 9%; mp 174-175°C; IR ν 3380, 1610 cm^{-1}; NMR ($CDCl_3$-D_2O) δ 4.48 (1H, d, J=3.5 Hz), 3.62 (2H, d d, J=3.5, 4.9 Hz).[8,9] The major threo isomer (5a) underwent smooth cyclization with TFA to afford the tetralin 7a [mp 280-281°C(dec); IR ν 1640 cm^{-1}; NMR δ 4.46 (1H, d, J=10.7 Hz), 4.33 (1H, d d, J=10.7, 2.0 Hz) with the expected thermodynamically more stable

C-1 aryl stereochemistry. Dethioketalization with HgO followed by low temperature basic work up[10] furnished the keto amide 8a [mp 164-166°C; IR ν 1675, 1640 cm^{-1}; NMR δ 4.48 (1H, d, J=6.1 Hz), 3.57 (1H, d d, J=6.1, 2.0 Hz)]. Brief exposure to warm TFA (epimerization at C-3) followed by in situ reduction with $NaBH_4$[11] gave the trans-anti-trans tetralin 9a [mp 154-155°C; IR ν 1630 cm^{-1}; NMR δ 4.26 (1H, d, J=10.7 Hz)]. Reduction of 9a with an 8-fold excess of $LiEt_3BH$ by a significant modification of Brown's procedure[12] yielded 10a as an inseparable mixture of phenol alcohols in ~1:1 ratio[13,14] [NMR δ 5.72, 5.67 (2 x s, D_2O-exch, ArOH), 3.86, 3.80 (2 x s, OMe), 3.75, 3.44 (2 x d d, J=11.3, 2.5 Hz, CH_2OH)]. Sequential mesylation, $LiEt_3BH$ reduction,[11] and methylation provided galcatin (2a).[15,16]

Umpolung of the two starting components to 3b and 4a for the tandem Michael addition-α-alkylation led to the synthesis of isogalcatin (2b) by an analogous sequence of reactions. The mixture of diastereoisomeric amide alcohols 5b,6b was obtained as above. 5b(threo): 87%; mp 161-162°C; IR ν 3400, 1608 cm^{-1}; NMR ($CDCl_3$-D_2O) δ 4.97 (1H, d, J=2.2 Hz), 3.49 (1H, d d, J=7.6, 2.2 Hz); 6b(erythro): 10%; mp 172-173°C; IR ν 3350, 1610 cm^{-1}; NMR ($CDCl_3$-D_2O) δ 4.61 (1H, d, J=2.9 Hz), 3.66 (1H, d d, J=4.9, 2.9 Hz). Using identical conditions, 5b was converted via 7b [72%; mp 200-202°C; IR ν 1635 cm^{-1}; NMR δ 4.49 (1H, d, J=11.0 Hz), 4.24 (1H, d d, J=11.0, 2.2 Hz)] and 8b [89%; mp 172-173°C (dec); IR ν 1672, 1640 cm^{-1}; NMR δ 4.46 (1H, d, J=4.9 Hz), 3.50 (1H, d d, J=4.9, 3.9 Hz)] into 9b [71%; mp 174-174.5°C; IR ν 1630 cm^{-1}; NMR δ 4.30 (1H, d, J=10.3 Hz)]. As in the case of 9a, $LiEt_3BH$ reduction of 9b delivered a 3:2 mixture of phenol alcohols 10b [61%; NMR δ 5.44, 5.34 (2 x s, D_2O-exch), 3.87, 3.63 (2 x s), 3.73, 3.47 (2 x d d, J=11.0, 2.0 Hz)]. Mesylation, $LiEt_3BH$ reduction, and methylation afforded isogalcatin (2b)[15,16] in 52% overall yield from 10b.[17]

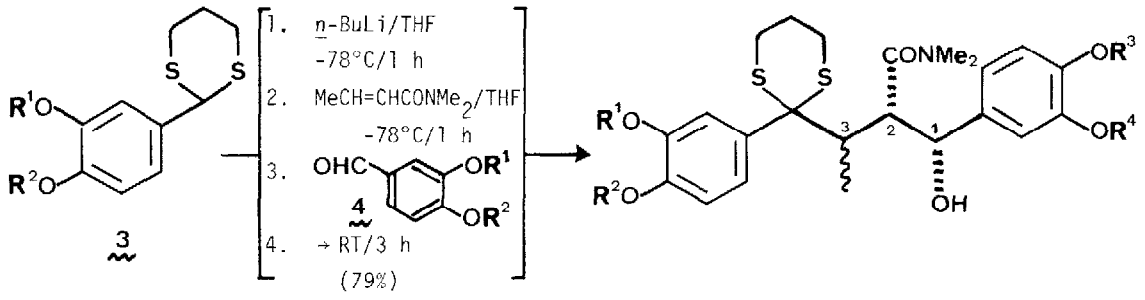
References and Footnotes

1. G.B. Mpango, K. Mahalanabis, Z. Mahdavi-Damghani, and V. Snieckus, Tetrahedron Lett., preceding communication in this issue.

2. a) T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring Compounds, Vol. 1: Acetogenins, Shikimates, and Carbohydrates," Academic Press, New York, 1975, p. 71; b) O.R. Gottlieb, Fortsch. Chem. Forsch., 35, 1 (1978).

3. F.E. Ziegler, I. Chliwner, K.W. Fowler, S.J. Kanfer, S.J. Kuo, and N.D. Sinha, J. Am. Chem. Soc., 102, 790 (1980); W.S. Murphy and S. Wattanasin, J.C.S., Chem. Comm., 262 (1980); E.R. Larson and R.A. Raphael, Tetrahedron Lett., 5041 (1979); K. Tomioka and K. Koga, ibid., 3315 (1979); E. Brown, M. Loriot, and J.-P. Robin, ibid., 1389 (1979); G. Büchi and P.-S. Chu, J. Org. Chem., 43, 3717 (1978); R.E. Damon, R.H. Schlessinger, and J.F. Blout, ibid., 41, 3772 (1976); A.S. Kende and L.S. Liebeskind, J. Am. Chem. Soc., 98, 267 (1976).

4. R. Stevenson and J.R. Williams, Tetrahedron, 33, 2913 (1977); R.S. Ward, P. Satyanarayana, L.R. Row, and B.V.G. Rao, Tetrahedron Lett., 3043 (1979).

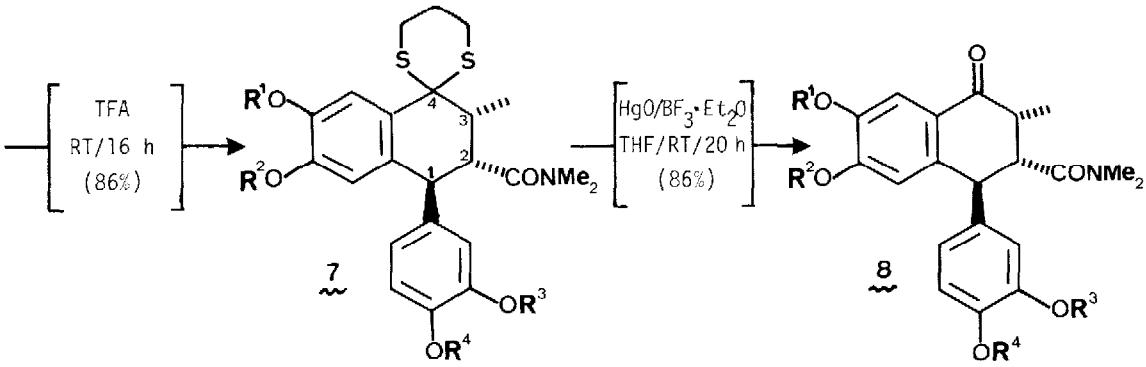


3

4

3,4 : a : $R^1 + R^2 = CH_2$
b : $R^1 = R^2 = Me$

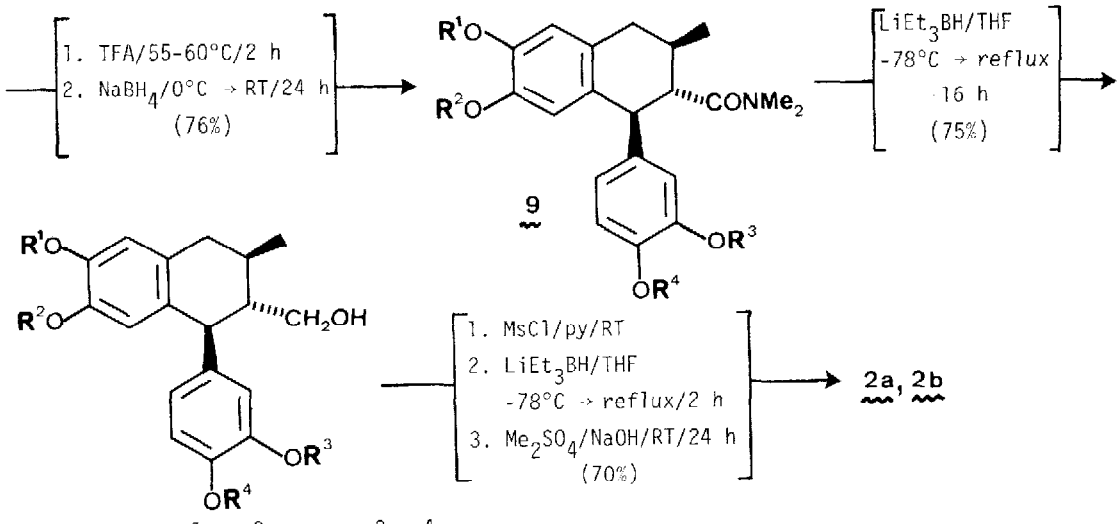
5a,5b : threo (β-C_3-Me)
6a,6b : erythro (α-C_3-Me)



7

8

5 – 9 : a: $R^1 + R^2 = CH_2$; $R^3 = R^4 = Me$
b: $R^1 = R^2 = Me$; $R^3 + R^4 = CH_2$



9

2a, 2b

10 : a: $R^1 + R^2 = CH_2$; R^3, R^4 = H,Me
b: R^1, R^2 = H,Me; $R^3 + R^4 = CH_2$

Scheme

5. P. Dombernowsky, N.I. Nissen, and V. Larsen, Cancer Chemother. Rep., 56, 71 (1972); F.M. Muggia, O.S. Selawry, and H.H. Hansen, ibid., 55, 575 (1971).

6. S.M. Kupchan, R.W. Britton, M.F. Ziegler, C.J. Gilmore, R.J. Restivo, and R.F. Bryan, J. Am. Chem. Soc., 95, 1335 (1973).

7. All new compounds showed spectral (IR($CHCl_3$), NMR($CDCl_3$), MS) and analytical data consistent with the proposed structures. Only the salient spectral features are given.

8. The observed stereoselectivity (5a) follows from the preferred Z-erythro transition state resulting from anti addition of ArCHO to the Z-amide enolate.

9. Collins oxidation of 5a and 6a gave two different ketones respectively:[7] threo: mp 146-147°C; IR ν 1670, 1640 cm^{-1}; NMR δ 5.22 (1H, d, J=7.6 Hz), 3.55 (1H, octet, J=7.6, 7.6 Hz); erythro: mp 196-197°C, IR ν 1685, 1630 cm^{-1}; NMR δ 5.29 (1H, d, J=7.8 Hz), 3.48 (1H, m). The very similar J's attest to the anti H_2-H_3-conformational preference for both ketones. Threo and erythro aldol products show analogous J value changes upon acetylation: H.O. House, D.S. Crumrine, A.Y. Teranishi, and H.O. Olmstead, J. Am. Chem. Soc., 95, 3310 (1973).

10. Room temperature work up resulted in partial epimerization to a mixture of C-3 stereoisomers of 8a which was less convenient to handle.

11. G.W. Gribble, W.J. Kelly, and S.E. Emery, Synthesis, 763 (1978).

12. H.C. Brown, S.C. Kim, and S. Krishnamurthy, J. Org. Chem., 45, 1 (1980).

13. Structural assignments of the two isomeric phenols of 10a and of 10b have not been made.

14. Extensive variation of reaction conditions showed that demethylation occurs prior to amide reduction presumably due to the hindered nature of the latter function. Aromatic ether cleavage has been previously observed with hydride reagents: T. Kametani et al., J. Org. Chem., 41, 2545 (1976).

15. O.R. Gottlieb, J.G.S. Maia, and M. Nilce de S. Ribeiro, Phytochemistry, 15, 773 (1976) and refs. therein.

16. Synthetic galcatin (2a) and isogalcatin (2b) were shown to be identical (mp, mixture mp, IR, NMR) with authentic materials. We are very grateful to Prof. Gottlieb, Sao Paulo and Prof. Adjangba, Toga for samples and copies of spectra and to Prof. R. Stevenson, Brandeis University for helpful correspondence.

17. This work was supported by the Natural Sciences and Engineering Research Council of Canada.

(Received in USA 18 August 1980)