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DIMETALATED TERTIARY SUCCINAMIDES. SYNTHESIS OF SEVERAL CLASSES OF LIGNANS INCLUDING THE MAMMALIAN URINARY LIGNANS ENTEROLACTONE AND ENTERODIOL

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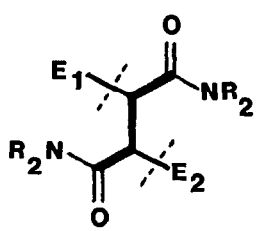
Summary. Reaction of dimetalated succinamides with benzyl halides and aromatic aldehydes provides short routes to diverse lignan natural products 2, 3, and 4a, including the human urinary metabolites (3d) and (2e)

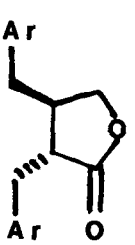
Within the scope of the synthetic methodology developed for 2,3-disubstituted succinamides 1[1] is the stereoselective introduction of aromatic aldehyde and benzyl units in identical [1, $E_1 = E_2$ = ArCH(OH) or $ArCH_2$] or mixed [1, $E_1 = ArCH_2$, E_2 = ArCH(OH)] fashion. Some of the resulting 1,4-diarylbutane systems are, in principle, convertible by simple transformations into 1,4-diarylbutane (2), dibenzylbutyrolactone (3) and 3,7-dioxabicyclo[3 3 0]octane (4) lignans [2,3] In this Letter, we report the realization of these conversions which, in practice, constitute short, efficient, and general syntheses of several classes of plant-derived lignans (2, 3, 4a)[2] as well as the first examples of the mammalian lignans, (±)-enterolactone (3d) and (±)-enterodiol (2e) [4,5] The recent discovery of the last two biogenetically interesting[6] substances coupled with their potential physiological implications has added a new dimension to the well-established position of lignans as natural products with a rich spectrum of biological activity [2,3a,7]



1

2

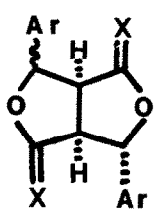
	X	Ar
a	OH	3,4-(OMe)$_2$C$_6$H$_3$
b	OH	3,4-(OCH$_2$O)C$_6$H$_3$
c	H	3,4-(OCH$_2$O)C$_6$H$_3$
d	OMe	3,4-(OMe)$_2$C$_6$H$_3$
e	OH	3-(OH)C$_6$H$_4$



3

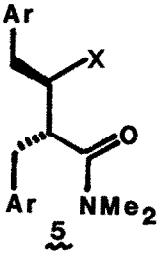
	Ar
a	3,4-(OMe)$_2$C$_6$H$_3$
b	3,4-(OCH$_2$O)C$_6$H$_3$
c	3-(OMe)C$_6$H$_4$
d	3-(OH)C$_6$H$_4$

2,3-Dibenzylated derivatives 5 were obtained according to the standard procedure:[1] threo:erythro(% yield): 5a: 20:1 (50); 5b: 15:1 (71); 5c: 8:1 (80).[8,9] Reduction with $LiEt_3BH$[10] (4.7 equiv./THF/↯/5 h) provided the amide alcohols[9,11] 5d (71%), 5e (83%), and 5f (66%) which were smoothly converted (TsOH/PhH/↯/4 h) into the butyrolactones[8] 3a (84%), 3b, (98%) and 3c (80%). 3a and 3b were shown to be identical with dimethylmatairesinol and hinokinin respectively.[12] Reduction ($LiAlH_4$/THF/RT/1 h/90%) of compounds 3a and 3b gave secoisolariciresinol dimethyl ether (2a)[13] and dihydrocubebin (2b).[13] Mesylation (MsCl/py/0°C) of 2b followed by reduction ($LiAlH_4$/THF/↯/1 h) (94% overall) afforded australobailignan-5 (2c).[12] The conversion of 2a into 2d has been reported.[2] This short sequence thus constitutes a general synthesis of structural types 2 and 3 from 5 in 27-50% overall yields. Demethylation (BBr_3/CH_2Cl_2/0°C) of 3c gave enterolactone (3d)[12] in 32% overall yield from N,N-dimethylsuccinamide. Reduction with $LiAlH_4$ as before gave enterodiol (2e) (80%).[12]



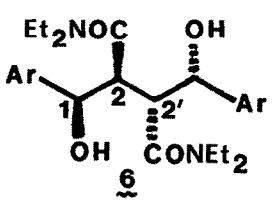
4

	X	Ar
a:	H_2	α-3,4-$(OMe)_2C_6H_3$
b:	O	α-3,4$(OMe)_2C_6H_3$
c:	O	β-C_6H_5
d:	O	α-C_6H_5

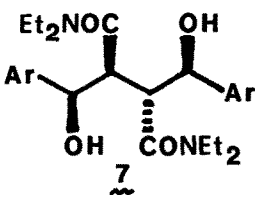


5

	X	Ar
a:	$CONMe_2$	3,4-$(OMe)_2C_6H_3$
b:	$CONMe_2$	3,4-$(OCH_2O)C_6H_3$
c:	$CONMe_2$	3-$(OMe)C_6H_4$
d:	CH_2OH	3,4-$(OMe)_2C_6H_3$
e:	CH_2OH	3,4-$(OCH_2O)C_6H_3$
f:	CH_2OH	3-$(OMe)C_6H_4$



6



7

a: Ar = Ph; b: Ar = 3,4-$(OMe)_2C_6H_3$

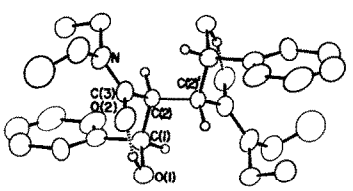
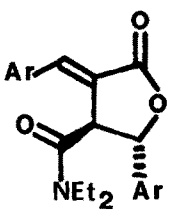


Figure: An ORTEP plot of the molecular crystal structure of compound 6a.



8

Ar

3,4-$(OMe)_2C_6H_3$

The reaction of dimetalated N,N-diethylsuccinamide (2.2 equiv LDA/TMEDA/THF/-78°C) with benzaldehyde (2.2 equiv/-78°C → rt/12 h) furnished a mixture of diasteriomers, 6a:7a (2:1) in 85% yield. The major isomer (6a), mp 184°C showed a simple NMR spectrum [$CDCl_3$-D_2O, δ 0.53 and 1.04 (12 H, 2 x t, J = 7 Hz), 2.8-3.5 (8 H, br m), 3.71 (2 H, s), 4.60 (2 H, s), 7.27 (10 H, s)] suggesting

a highly symmetrical structure The syn-anti-syn stereochemistry[14] of 6a was revealed by x-ray crystallographic analysis (Figure) [15,16] Similarly, condensation with veratraldehyde led in 72% yield to a mixture of 6b 7b (3 1) [8] The syn-stereoselectivity at $C_{1,2}$ and $C_{1',2'}$ follows the accepted features of the aldol condensation[17] under thermodynamic control (minimal non-bonded interaction with Ar in pseudo-axial orientation),[18] while the anti $C_{2,2'}$ configuration may be rationalized by a least hindered approach of the second PhCHO to the 1 1 adduct monoenolate

Refluxing of the major diasteriomer 6a in HOAc (2 h) and MeOH/HCl (40 min) gave the trans-2,6- and cis-2,6-diphenyl bislactone 4c (85%)[13] and 4d (65%)[12] respectively Under extended reflux in HOAc (18 h), the tetramethoxy adduct 6b was converted into a mixture of 4b (35%)[13] and the dehydro monolactone 8 (65%) [8] In the transformations 6a → 4b-c, epimerization at C_2 ($C_{2'}$) is a minimal requirement, the diaryl stereochemistry in 4b, 4d may be a consequence of thermodynamic stability The expected enhanced formation of carbonium ions in 6b may be responsible for the product distribution disfavoring 4b. These mechanistic implications are under further study Bislactones of this type have been converted into naturally-occurring lignans, e g 4b → 4a (eudesmin).[3d]

Dimetalated succinamides provide an efficient synthetic alternative to existing methodology[3b-d,19] for the construction of diverse lignan natural products [20]

References and Footnotes

1. *Mahalanabis, K.K.; Mumtaz, M., Snieckus, V., Tetrahedron Lett. preceding communication in this issue.*
2. *Rao, C B S , ed. "Chemistry of Lignans", Andhra University Press, Andhra Psadesh, India, 1978.*
3. *(+)- and (-)-4, X=O, Ar = 3,4-$(OH)_2C_6H_3$ are unique bislactone lignans isolated from a cultured mushroom: a) Kumada, Y., Naganawa, H., Takeuchi, T., Umezawa, H., Yamashita, K., Watanabe, K. J. Antibiotics 1978, 31, 105 Synthesis· b) Brownbridge, P., Chan. T.-H. Tetrahedron Lett. 1980, 3427; c) Taylor, E.C et al. J. Org. Chem. 1981, 46, 3078, d) Pelter, A. et al. J.C S. Perkin Trans I, 1982, 175.*
4. *Structure· a) Stitch, S.R.; Toumba, J.K., Groen, M B , Funke, C.W., Leemhuis, J ; Virk, J.; Woods, G.F Nature 1980, 287, 738, b) Setchell, K.D.R.; Lawson, A M , Mitchell, F L., Aldercreutz, H., Kirk, D.N., Axelson, M ibid. 1980, 287, 740.*
5. *Synthesis a) Groen, M.B., Leemhuis, J. Tetrahedron Lett. 1980, 5043, b) Cooley, G., Farrant, R.D ; Kirk, D N , Wynn, S ibid. 1981, 349, c) Pelter, A., Satyanarayana, P., Ward, R.S. ibid. 1981, 1549; d) Ganeshpure, P.A.; Stevenson, R. Chem. Ind. (London) 1981, 778.*
6. *See Hatam, N A R.; Whiting, D.A. J.C.S. Perkin I, 1982, 461.*
7. *Antitumor. Hartwell, J L. Cancer Treat. Rep. 1976, 60, 1031, Barclay, A.S , Perdue, Jr., R E. ibid. 1976, 60, 1081. Germination inhibition Cooper, R.; Levy, E.C., Lavie, D.*

J.C.S. Chem. Commun. **1977**, 794. Enzyme inhibition: ref. 3a; Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, U.; Nishibe, S.; Hisada, S. *Chem. Pharm. Bull. Jpn.* **1981**, *29*, 3586. Antifugal: Fernandez, S., Hurtado, L.M., Hernandez, F. *in* Geissbuhler, H. ed. *Adv. Pesticide Sc. Pt. 2*, Pergamon Press, Oxford, **1978**, p. 351.

8. All new compounds show analytical and spectral (ir,nmr,ms) data in accord with their structures. Yields are of isolated products.
9. *Threo:erythro* assignments were inferred from comparison with the diasteriomers of the parent diamide **5**, X = $CONMe_2$, Ar = C_6H_5 of established stereochemistry (ref. 1).
10. Brown, H.C.; Kim, S.C.; Kirshnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.
11. This result implies protection of one of the amide functions as the enolate by the highly basic hydride reagent.
12. Established by comparison of physical and spectral data with those reported in the literature: **2c**: oil, Taylor, W.C.; Ritchie, E.; Murphy, S.T. *Austr. J. Chem.* **1975**, *28*, 81: **2e**: mp 175-176°C, lit (5a) mp 171-173°C; **3a**: mp 118-119°C, lit mp 126-127°C, Takaoka, D. *et al. Nippon Kagaku Kaishi* **1975**, 2192; *Chem. Abstr.* **1976**, *84*, 71488k; **3b**: mp 108°C, lit mp 107-108°C, Haworth, R.D.; Woodcock, D. *J.C.S.* **1938**, 1985; **3d**: gum, lit (5a) mp 141-143°C, (5b) gum; **4b**: mp 208°C, lit (3b) mp 208.5-209°C; **4d**: mp 171-172°C, lit (3b) mp 181-183°C.
13. Identified by comparison (tlc, mixture mp, ir, nmr) with authentic samples: **2a**: mp 124-125.5°C, lit mp 124-125°C, Takaoka, D. *et al. loc. cit.*; **2b**: mp 106°C, lit mp 104°C, Batterbee, J.E.; Burden, R.S.; Crombie, L.; Whiting, D.A. *J.C.S.(C)*, **1969**, 2470; **4c**: mp 184°C, lit (4b) mp 178-180°C.
14. We adopt the *syn,anti* terminology as defined by Masamume, S.; Ali, Sk. A.; Suitman, D.L.; Garvey, D.S. *Angew Chem. Int. Ed. Engl.* **1980**, *19*, 557.
15. The analysis was economically performed in this department by Dr. N. Taylor. Atomic coordinates have been deposited with the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, England CB2 1EW. Crystal Data: $C_{26}H_{18}N_2O_4$, M.Wt. 440.59, Triclinic, a = 11.619(3), b = 14.722(4), c = 14.976(6) Å, α = 96.65(3), β = 91.00, γ = 96.96(2)°. Space Group $P\bar{1}$, Z = 4. The structure was solved by Direct Methods (Multan80) using 3915 $3\sigma(I)$ observed reflections ($2\theta \leq 46°$) collected on a Syntex $P2_1$ diffractometer. The structure has been refined by full-matrix, least-squares methods to a current R of 0.101. The asymmetric unit contains four half-molecules sitting across centres of symmetry (1,½,0), (1,0,½), (½,0,0) and (½,½,½). All ethyl groups exhibit disorder.
16. The minor isomer (**7a**) mp 126°C is tentatively assigned the *syn-anti-anti* stereochemistry on the basis of its complex NMR spectrum ($CDCl_3$-D_2O δ 3.52 (dd, J = 2.5, 9.6 Hz), 3.95 (dd, J = 4.5, 9.6 Hz), 4.73 (d, J = 2.5 Hz), 4.98 (d, J = 4.5 Hz) and its hydrogenolysis (H_2/Raney Ni/EtOH) to *erythro*-2,3-dibenzyl-N,N-diethylsuccinamide which was also obtained, as expected, by hydrogenolysis of the major isomer (**6a**).
17. Bartlett, P.A. *Tetrahedron* **1980**, *36*, 2.
18. Under kinetic control (-78°C/5 min), the ratio of **6a**:**7a** is inverted (1:2).
19. E.G. based on: Stobbe condensation: refs. 2, 5a-b; butyrolactone alkylation: ref. 5d, Ganesphure, P.A.; Stevenson, R. *J.C.S. Perkin Trans. I*, **1981**, 1681; tandem Michael addition-α-alkylation onto butenolide: ref. 5c, Tomioka, K. Koga, K. *Tetrahedron Lett.* **1979**, 652 and refs. therein.
20. We thank NSERC of Canada for continuing financial support, Jadavpur University, Calcutta for a leave of absence to K.K.M, Drs. Chan, Crombie and Takaoka for samples, and Drs. Taylor and Setchell for spectra.

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