Tetrahedron Letters,Vol.27,No.42,pp 5147-5150,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF UNSYMMETRICAL SPERMINE ALKALOIDS OF THE HOMALIUM GROUP

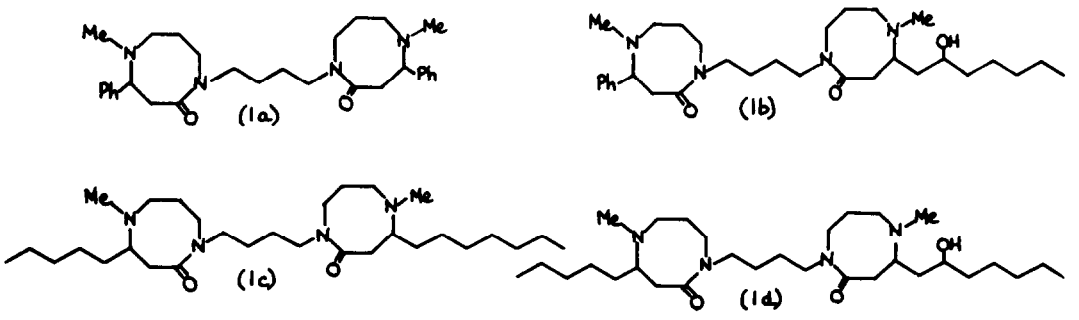
Leslie Crombie*, Raymond C.F. Jones*, and David Haigh

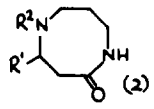
Department of Chemistry, The University,
Nottingham, NG7 2RD, U.K.

Summary: Spermine alkaloids homaline, hopromalinol, hopromine, and hoprominol are prepared by sequential coupling of 4-substituted 5-methyl-1,5-diazacyclooctan-2-ones, available by transamidation from 4-substituted azetidin-2-ones, to 1,4-dichlorobut-2-ene.

Homalium alkaloids (1a-d), isolated from the leaves of Homalium pronyense (Flacourtiaceae), have unique bis-eight-membered lactam structures.[1] They are based biogenetically on combination of two residues (fatty or cinnamic acid) with the polyamine spermine. We report here an approach leading to the first syntheses of the unsymmetrical alkaloids hopromalinol (1b), hopromine (1c), and hoprominol (1d), and to a new synthesis of the parent compound homaline (1a).[2]

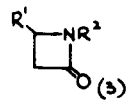
The four building blocks required were the eight-membered azalactams (2a-d), prepared by our recently reported transamidation sequence[3] from the corresponding β-lactams (3a-d). Thus 4-phenylazetidin-2-one (3a) (from styrene and N-chlorosulphonyl isocyanate[4]), and 4-pentyl- and 4-heptyl-azetidin-2-ones [(3b) and (3c) respectively], (from Grignard addition to 4-phenylsulphonyl-azetidin-2-one,[5] yields 96 and 71%) were converted into the corresponding N-(3-chloropropyl)-β-lactams (4a) (71%), (4b) (80%), and (4c) (72%) on treatment with 1-bromo-3-chloropropane and powdered KOH in dimethyl sulphoxide at 20°C.[6]





(2)

(2) a; R^1 = Ph, R^2 = H
b; R^1 = $[CH_2]_4Me$, R^2 = H
c; R^1 = $[CH_2]_6Me$, R^2 = H
d; R^1 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^2 = H
e; R^1 = Ph, R^2 = Me
f; R^1 = $[CH_2]_4Me$, R^2 = Me
g; R^1 = $[CH_2]_6Me$, R^2 = Me
h; R^1 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^2 = Me
i; R^1 = Ph, R^2 = CO_2CH_2Ph
j; R^1 = $[CH_2]_4Me$, R^2 = CO_2CH_2Ph
k; R^1 = $[CH_2]_6Me$, R^2 = CO_2CH_2Ph
l; R^1 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^2 = CO_2CH_2Ph



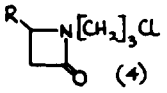
(3)

(3) a; R^1 = Ph, R^2 = H
b; R^1 = $[CH_2]_4Me$, R^2 = H
c; R^1 = $[CH_2]_6Me$, R^2 = H
d; R^1 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^2 = H
e; R^1 = $CH_2CO[CH_2]_4Me$, R^2 = H
f; R^1 = $CH_2CH(OH)[CH_2]_4Me$, R^2 = H
g; R^1 = $CH_2CH(OH)[CH_2]_4Me$, R^2 = $SiMe_2Bu^t$
h; R^1 = $CH_2CH=CH_2$, R^2 = H
i; R = CH_2CH-CH_2 (O), R^2 = $SiMe_2Bu^t$

The fourth β-lactam (3d) was prepared by treatment of 4-acetoxyazetidin-2-one with the trimethylsilyl enol ether (5) (from 2-heptanone, $LiNPr^i_2$/THF, -78°C; Me_3SiCl) and zinc chloride in dichloromethane[7] to produce 4-(2-oxoheptyl)-azetidin-2-one (3e)[8] (83%), followed by reduction ($NaBH_4$-MeOH) to the 4-(2-hydroxyheptyl)-β-lactam (3f) (93%). t-Butyldimethylsilylation of (3f) afforded the N-silyl derivative (3g), the most efficient procedure (99%) employing n-butyl-lithium and t-butyldimethylsilyl chloride in tetrahydrofuran (THF). The unusual rearrangement to the O-silylazetidinone (3d) was achieved by treatment of (3g) with lithium dibutylcuprate (Bu^nLi, CuI) in THF at -20°C (86%). Alternatively, silylation and migration could be performed in 'one-pot' by successive addition to (3f) in THF of Bu^nLi, Bu^tMe_2SiCl, and $LiCuBu^n_2$ (77%). The cuprates appeared uniquely effective in the silyl group migration, as (3g) was unaffected by various basic reagents or by copper (I) salts.
An alternative route to β-lactam (3d) also originated with 4-acetoxyazetidin-2-one. Conversion into the 4-allyl derivative (3h) (allyltrimethylsilane, $BF_3.OEt_2$, CH_2Cl_2; 76%)[9] followed by N-silylation (Bu^tMe_2SiCl, diazabicycloundecane, MeCN; 94%) and epoxidation gave the epoxy-β-lactam (3i) (3-chloroperoxybenzoic acid; 90%). Epoxide opening with lithium dibutylcuprate (THF, -20°C) was accompanied by the migration of the t-butyldimethylsilyl group to afford (3d) (80%). Alkylation of the O-silylazetidinone (3d) with 1-bromo-3-chloropropane (powdered KOH, THF, $Bu^n_4NHSO_4$, 20°C)[10] finally afforded the fourth N-(3-chloropropyl)-β-lactam (4d) (77%).

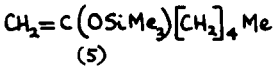
Treatment of chlorides (4a-d) with liquid ammonia in a sealed tube (20°C, 6 days) gave directly the corresponding eight-membered azalactams (2a-d) in excellent yields (96, 96, 85, and 79% respectively). Reductive methylation[11] of the amino nitrogen in these compounds (H_2CO, $NaBH_3CN$) converted them into the N-methyl azalactams (2e-h) (97, 77, 83, and 92%, respectively). To mask the amino nitrogen, the N-benzyloxycarbonyl derivatives (2i-l) were also prepared from (2a-d).

Various unsuccessful attempts to couple the N-(4-bromobutyl)azalactams

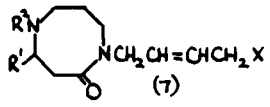


(4)

(4) a; R = Ph
b; R = $[CH_2]_4Me$
c; R = $[CH_2]_6Me$
d; R = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$

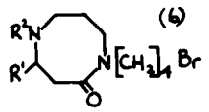


(5)



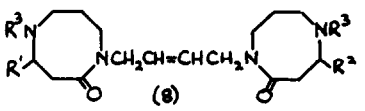
(7)

(7) a; R^1 = Ph, R^2 = CO_2CH_2Ph, X=Br
b; R^1 = $[CH_2]_4Me$, R^2 = CO_2CH_2Ph, X=Br
c; R^1 = Ph, R^2 = Me, X=Cl
d; R^1 = $[CH_2]_4Me$, R^2 = Me, X=Cl
e; R^1 = $[CH_2]_6Me$, R^2 = Me, X=Cl



(6)

(6) a; R^1 = Ph, R^2 = Me
b; R^1 = $[CH_2]_4Me$, R^2 = Me
c; R^1 = Ph, R^2 = CO_2CH_2Ph



(8)

(8) a; R^1 = R^2 = Ph, R^3 = CO_2CH_2Ph
b; R^1 = Ph, R^2 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^3 = CO_2CH_2Ph
c; R^1 = $[CH_2]_4Me$, R^2 = $[CH_2]_6Me$, R^3 = CO_2CH_2Ph
d; R^1 = R^2 = Ph, R^3 = Me
e; R^1 = Ph, R^2 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^3 = Me
f; R^1 = $[CH_2]_4Me$; R^2 = $[CH_2]_6Me$, R^3 = Me
g; R^1 = $[CH_2]_4Me$, R^2 = $CH_2CH(OSiMe_2Bu^t)[CH_2]_4Me$, R^3 = Me

(6a-c) [derived from (2e), (2f), and (2i)] to a further molecule of azalactam dictated the use of the more reactive 1,4-dihalobut-2-enes as the four-carbon link. Thus the N-(4-bromobut-2-enyl) compounds (7a) and (7b) were prepared from (2i) and (2j), respectively, and (E)-1,4-dibromobut-2-ene (NaH, THF). Coupling of (7a) with lactams (2i) and (2l), and of (7b) with lactam (2k), all by the NaH-THF procedure, then led to the corresponding bis-lactams (8a) (66%), (8b) (21%), and (8c) (47%) which contain the carbon skeletons of homaline (1a) hopromalinol (1b), and hopromine (1c). The syntheses of (1a-d) were, however, best completed from the N-methyl azalactams (2e-h). Treatment of (2e-g) with (Z)-1,4-dichlorobut-2-ene [$KN(SiMe_3)_2$, THF] afforded the N-(4-chlorobut-2-enyl) lactams (7c) (53%), (7d) (40%), and (7e) (28%), and coupling [$KN(SiMe_3)_2$-NaH, THF] of these chlorides with an appropriate eight-membered azalactam produced the required bis-lactam frameworks. Thus (7c) with (2e) afforded (8d) (36%), and with (2h) gave (8e) (41%), whilst (7e) with (2f), and (7d) with (2h) led to (8f) (29%) and (8g) (20%), respectively. Finally the alkenes (8d-g) were hydrogenated (1 atmosphere, PtO_2, HCl-MeOH, 20°C) to produce the alkaloids homaline (1a) (95%), hopromalinol (1b) (91%), hopromine (1c) (98%), and hoprominol (1d) (99%), each as a mixture of stereoisomers.[12] The t-butyldimethylsilyl protecting group is removed under these conditions.

We thank the S.E.R.C. for support and Dr. M. Païs for spectral data on the natural alkaloids.

References

1. M. Païs, R. Sarfati, F.-X. Jarreau, and R. Goutarel, Tetrahedron, 1973, 29, 1001.
2. For other synthetic studies see: L. Crombie, R.C.F. Jones, A.R. Mat-Zin, and S. Osborne, J.Chem.Soc., Chem.Commun., 1983, 960, and refs. therein.
3. L. Crombie, R.C.F. Jones, S. Osborne, and A.R. Mat-Zin, J.Chem.Soc., Chem.Commun., 1983, 959.
4. R. Graf, Liebigs Ann.Chem., 1963, 661, 111.
5. T. Kobayashi, N. Ishida, and T. Hiraoka, J.Chem.Soc., Chem.Commun., 1980, 736.
6. R.A.W. Johnstone and M.E. Rose, Tetrahedron, 1979, 35, 2169.
7. P.J. Reider, R. Rayford, and E.J.J. Grabowski, Tetrahedron Lett., 1982, 23, 379.
8. New compounds gave spectra consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.
9. G.A. Kraus and K. Neuenschwander, J.Chem.Soc., Chem.Commun., 1982, 134.
10. D. Reuschling, H. Pietsch and A. Linkies, Tetrahedron Lett., 1978, 615.
11. R.F. Borch and A. Hassid, J.Org.Chem., 1972, 37, 1673.
12. No further separation was attempted. The absolute configurations of (1b-d) are unknown.

(Received in UK 4 August 1986)