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A CONCISE, PALLADIUM-CATALYZED APPROACH TO (±)-LYSERGIC ACID

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Summary: A new and straightforward route to (±)-lysergic acid (1) from the tricyclic ketone 2 is described involving the palladium-catalyzed coupling of the vinyl triflate 3 with the olefin 5 as the key step.

Lysergic acid (1) is pivotal among ergot alkaloids both from the synthetic viewpoint and because of its remarkable pharmacological potential.[1]

The importance of 1 as a synthetic target is witnessed by the occurrence of several total syntheses,[2] three of which have appeared during the last four years.

Following the first report by Woodward in 1956,[2i] the tricyclic ketone 2 (Kornfeld's ketone) has been utilized as the central intermediate in two related procedures formally based on the mechanism proposed for the ready epimerisation of lysergic and isolysergic acids.[2a,g]

The aminodienoic ester 7, transiently produced in nine steps from 2, has indeed been shown to afford a mixture of the tetracyclic isomers 9, 10, and 11 as a result of spontaneous cyclisation.[2g]

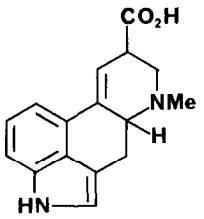
Established oxidative addition of vinyl triflates to palladium(0) and ability of the resulting vinylpalladium(II) species to undergo Heck-type reaction[3] have prompted us to devise a novel and more expeditious route to 7 and hence to the 2,3-dihydrolysergic system.

To this end, Kornfeld's ketone 2 has been converted to the vinyl triflate 3[4] with triflic anhydride and 2,6-di-tert-butyl-4-methylpyridine in 91% yield.

Preliminary olefination experiments on 3, following conditions described in ref. 3c and using methyl acrylate and methyl methacrylate as the olefins, led to the formation of the dienoic ester 4[5] in 61% yield and to an approximately 1:1 mixture of compounds 5[6] and 8[6] in 49% yield, respectively.

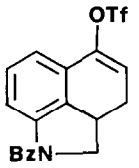
The ester 4 has been previously obtained by Ramage[2g] in four steps from 2 and was shown to constitute a promising intermediate in the synthesis of modified lysergic systems via intermolecular Diels-Alder cycloadditions.

Having ascertained the feasibility of 3 to undergo vinylation reactions in synthetically useful yields, we turned our attention to the synthesis of a suitable bifunctionalised olefin

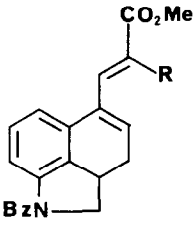


1

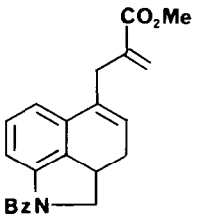
2
(Bz=C6H5CO)



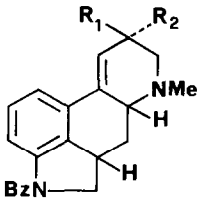
3
(OTf=OSO2CF3)



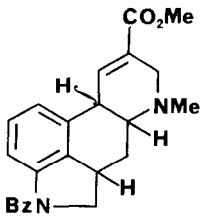
4, R=H
5, R=Me
6, R=CH2N(Boc)Me
7, R=CH2NHMe



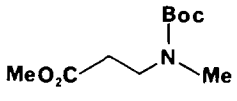
8



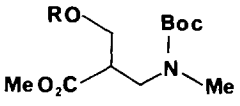
9, R1=CO2Me; R2=H
10, R1=H; R2=CO2Me



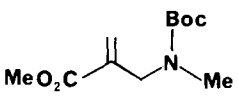
11



12
(Boc=tBuOCO)



13, R=H
14, R=SO2Me



15

which would be able to afford an immediate precursor of 7 in a single step.

The envisaged building block 15[7] was obtained from methyl 3-(N-tert-butoxycarbonyl-N-methyl)-aminopropionate (12)[8] by a three-steps sequence comprising trapping of the anion of 12 (LDA, THF, -78 °C) with formaldehyde to give the hydroxymethyl derivative 13 (53% yield),[9] conversion of 13 into the mesylate 14 (MsCl, Et_3N, CH_2Cl_2, r.t.), and elimination reaction on crude 14 (DBU, benzene, r.t., 74% yield from 13).

Palladium-catalyzed reaction between 3 and 15 (1.1 equiv.; $Pd(OAc)_2$, 3 mol%; PPh_3, 6 mol%; Et_3N, 2.5 equiv.; DMF, 60 °C, 24 h) gave the desired aminodienoate 6[10] as the main coupling product in 26% yield.[11] Deshielding of acyclic proton β to the ester function into the aromatic region was consistent with the E configuration shown for 6 and required for the final step.[12]

Indeed, cleavage of the tert-butoxycarbonyl group (2.5 N HCl in AcOEt, 1.5 h, r.t.), followed by treatment with $NaHCO_3$, afforded a 1.7:1 mixture (^1H NMR analysis) of the two epimeric unsaturated esters 9 and 10 in 60% yield.[13] Crystallisation of the mixture from ethyl acetate afforded homogeneous methyl 1-benzoyl-2,3-dihydrolysergate (9): mp 165-167 °C (lit.[2a,b,g] 165-168 °C); IR ($CHCl_3$) 1729, 1634, 1603, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (q, 1H, J=11.7 Hz), 2.51 (s, 3H), 2.42-2.61 (m, 1H), 2.70 (t, 1H, J=11.4 Hz), 3.06 (br dd, 1H, J=11.7 Hz, 3.0 Hz), 3.28 (dd, 1H, J=11.7 Hz, 6.0 Hz), 3.35-3.50 (m, 1H), 3.69 (t, 1H, J=11.0 Hz), 3.60-3.70 (m, 1H), 3.76 (s, 3H), 4.1-4.6 (br, 1H), 6.55 (br s, 1H), 7.16-7.63 (m, 8H).

From the ^1H NMR spectrum of the mixture of 9 and 10, the following peaks were assignable to methyl 1-benzoyl-2,3-dihydroisolysergate (10): δ 1.42 (q, 1H, J=11.7 Hz), 2.49 (s, 3H), 2.58 (dd, 1H, J=11.7 Hz, 5.0 Hz), 2.88 (br dd, 1H, J=11.7 Hz, 2.0 Hz), 3.18 (br t, 1H), 3.44 (d, 1H, J=11.7 Hz), 3.68 (t, 1H, J=11.0 Hz), 3.72 (s, 3H).

^1H NMR values of both 9 and 10 are in agreement with those reported by Ninomyia,[2b] Rebek,[2c] and Ramage.[2g]

Homogeneous 8β-ester (9) yielded a 1.7:1 mixture of the epimeric esters 9 and 10 upon being refluxed in methanol for 3 h. This isomerisation mixture did not coincide with that (3:1) reported by Ninomyia[2b] and Rebek.[2c] At 40 °C an equilibrium mixture of 9 and 10 in the ratio 1.3:1 was observed (equilibration time: 4 h).

Since the 8β-ester 9 has already been converted into (±)-lysergic acid,[2g,i] the present work constitutes a novel total synthesis of (±)-lysergic acid, which competes favourably with most of other total syntheses in terms of number of steps and of overall yield.

References and Notes

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3. (a) W.J. Scott, M.R. Peña, K. Swärd, S.J. Stoessel, and J.K. Stille, J. Org. Chem., 50, 2302 (1985); (b) W. Harnish, E. Morera, and G. Ortar, J. Org. Chem., 50, 1990 (1985); (c) S. Cacchi, E. Morera, and G. Ortar, Tetrahedron Lett., 2271 (1984).
4. 3: mp 165-166 °C (CH_2Cl_2/MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (dt, 1H, J=15.0 Hz, 2.0 Hz),

2.72 (m, 1H), 3.69 (m, 1H), 3.81 (t, 1H, J=10.9 Hz), 4.43 (m, 1H), 5.97 (dd, 1H, J=6.0 Hz, 2.0 Hz), 6.90-7.77 (m, 8H).

5. 4: mp 125-128 °C (CH_2Cl_2/hexane, lit.[2g] mp 131-133 °C); ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.0-2.9 (m, 2H), 3.3-3.9 (m, 2H), 3.77 (s, 3H), 4.43 (m, 1H), 6.2-6.5 (m, 2H), 7.0-7.8 (m, 9H). These values are in agreement with those reported by Ramage.[2g]
6. From the ^{1}H NMR spectrum (90 MHz, $CDCl_3$) of the mixture of 5 and 8, the following peaks were assignable to 5: δ 1.95 (d, 3H, J=1.5 Hz), 3.80 (s, 3H), 6.03 (br d, 1H, J=6 Hz), 6.82 (m, 1H); the following peaks were conversely attributable to 8: δ 3.47 (m, 2H), 3.77 (s, 3H), 5.55 (br s, 1H), 5.83 (br d, 1H, J=6 Hz), 6.25 (br s, 1H).
7. 15: oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.85 (s, 3H), 3.77 (s, 3H), 4.40 (br s, 2H), 5.58 (br s, 1H), 6.30 (br s, 1H).
8. Prepared in 75% yield from methyl 3-methylaminopropionate /R.W. Holley and A.D. Holley, J. Am. Chem. Soc., 71, 2124 (1949)/ and di-tert-butyl dicarbonate, following the procedure used for the preparation of the corresponding ethyl ester /T. Kurihara, T. Terada, S. Satoda, and R. Yoneda, Chem. Pharm. Bull. Jpn., 34, 2786 (1986)/: bp 85-87 °C (1.5 mm Hg); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.53 (t, 2H, J=7 Hz), 2.85 (s, 3H), 3.50 (t, 2H, J=7 Hz), 3.67 (s, 3H).
9. 13: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.76 (m, 1H), 2.83 (s, 3H), 3.47 (dd, 2H, J=14.0 Hz, 5.6 Hz), 3.83 (dd, 2H, J=11.3 Hz, 4.8 Hz), 3.70 (s, 3H).
10. 6: foam; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.26 (br t, 1H, J=15.6 Hz), 2.50-2.80 (m, 1H), 2.65 (s, 3H), 3.44-3.62 (m, 1H), 3.68-3.90 (m, 1H), 3.80 (s, 3H), 4.04-4.60 (m, 3H), 6.00 (br d, 1H, J=6.0 Hz), 6.70-7.77 (m, 9H).
11. Attempts to improve the yield of 6 by performing the vinylation reaction under phase-transfer conditions /T. Jeffery, Tetrahedron Lett., 2667 (1985); T. Jeffery, J. Chem. Soc., Chem. Commun., 1287 (1984)/ met with failure.
12. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed., Pergamon Press, Oxford, 1969, pp 184-185.
13. The failure to isolate compound 11 from the cyclisation of intermediate 7 may be explained by the aforementioned[2g] facile rearrangement of 11 to 10.

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