The Formation of Optically Active 1,3-Disubstituted and 1,1,3-Trisubstituted Tetrahydro-β-carbolines using a Modified Pictet–Spengler Reaction

Patrick D. Bailey,* Sean P. Hollinshead, and Zbigniew Dauter

Department of Chemistry, University of York, Heslington, York Y01 5DD, U.K.

Optically active 1,3-disubstituted and 1,1,3-trisubstituted 1,2,3,4-tetrahydro-β-carbolines were formed by the reaction of various N^{α},N^{in}-substituted (*S*)-tryptophan methyl esters with methyl propynoate or dimethyl butynedioate respectively; the stereoselectivity of the reactions is reported.

Because of the wide range of alkaloids that contain the tetrahydro-β-carboline unit, there is considerable interest in synthetic routes to these tricyclic systems, particularly those in which optically active 1,3-disubstituted tetrahydro-β-carbolines are formed.[1]

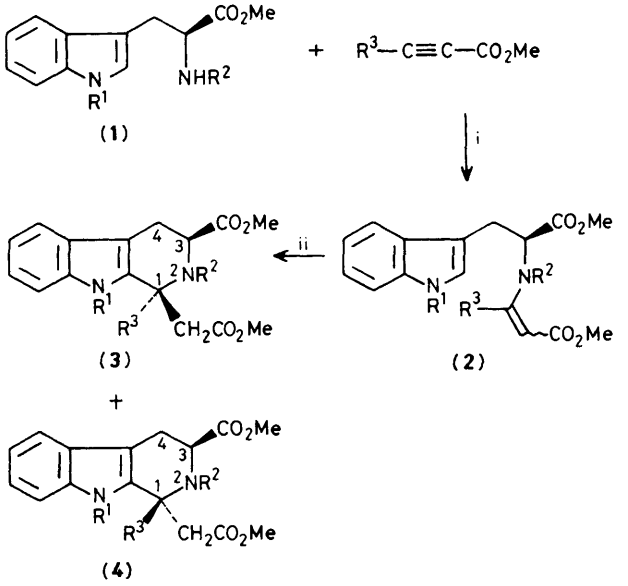
A recent modification of the much used Pictet–Spengler reaction[2] involves the addition of tryptamine to methyl propynoate or dimethyl butynedioate; acidification of the resulting enamines leads to the formation of 1-substituted or 1,1-disubstituted tetrahydro-β-carbolines.[3] We now report the similar reaction of (*S*)-tryptophan methyl esters (**1**) with conjugated alkynoates, leading to the formation of 1,3-disubstituted or 1,1,3-trisubstituted tetrahydro-β-carbolines (Scheme 1).

We found that the formation of enamines (**2**) from dimethyl butynedioate and (**1**) proceeded rapidly and cleanly, as expected (*cf.* ref. 3). In contrast, similar reactions using methyl propynoate as the Michael acceptor were very

Table 1.

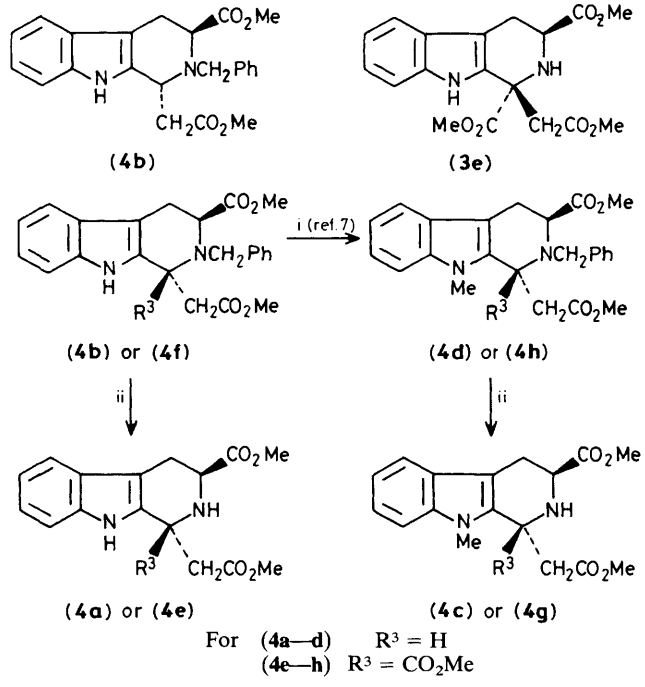
Compound	R^1	R^2	R^3	Formation of enamine (2)	Yield of (3) + (4)/%[a]	Purification of (3) + (4)[b]	Ratio of (3):(4)[c]	Separation of (3) from (4)[d]
a	H	H	H	60 h	50	C	71:29	R
b	H	CH_2Ph	H	120 h	45	C	27:73	R
c	Me	H	H	24 h	44	C	37:63	R
d	Me	CH_2Ph	H	240 h	25	C	28:72	N
e	H	H	CO_2Me	5 min	91	P	68:32	N
f	H	CH_2Ph	CO_2Me	10 min	51	C	59:41	C
g	Me	H	CO_2Me	10 min	99	P	55:45	C
h	Me	CH_2Ph	CO_2Me	5 min	—	M	—	—

[a] Yield of isolated product is given. All products were consistent with ^1H and ^{13}C n.m.r. spectra; neither mass spectrometry nor t.l.c. indicated the presence of any impurities. [b] Purification: C, flash chromatography; P, pure after NaOH (aq.) wash; M, complex mixture. [c] Ratio of (3):(4) was determined by the average relative intensity of the ^{13}C n.m.r. peaks from diastereotopic carbon atoms. [d] Separation of diastereoisomers: R, recrystallisation; C, flash chromatography; N, not separated.



R^1 = H or Me, R^2 = H or CH_2Ph, R^3 = H or CO_2Me

Scheme 1. *Conditions:* i, $CHCl_3$, room temp.; ii, TFA–$CHCl_3$, room temp.



Scheme 2. Reagents, i, NaH in dimethylformamide then MeI; ii, H_2/Pd–C. All of the reactions yielded single diastereoisomers.

sluggish, and went to completion only after 1—10 days. The reactions were conveniently followed by t.l.c. and ^1H n.m.r. spectroscopy; the latter was particularly informative in the δ 4—8 region, where peaks characteristic of the *cis* and *trans* enamine vinylic protons were apparent.[4] These enamines (**2**) were not isolated, but the addition of trifluoroacetic acid (TFA) effected rapid cyclisation (reaction complete in <15 min) to give the desired tetrahydro-β-carbolines (**3**) and (**4**).

Although ^{13}C n.m.r. spectroscopy clearly indicated the presence of two diastereoisomers in all of the purified products, unambiguous assignment of the stereochemistries from the ^{13}C n.m.r. data was not possible for our compounds.† After the separation of several pairs of diastereoisomers by recrystallisation or flash chromatography,[6] a single crystal *X*-ray structure determination was carried out on one of the methyl propynoate adducts (**4b**) and on one of the dimethyl butynedioate adducts (**3e**).‡ The latter was prepared as the pure diastereoisomer by the hydrogenolysis of the

† It has been shown that the chemical shifts of C-1 and C-3 in *trans* 1,3-disubstituted tetrahydro-β-carbolines are consistently at higher field than those of the corresponding *cis* isomers.[5] However, for two of our compounds for which this analysis should have been straightforward [(**3b**)/(**4b**) and (**3d**)/(**4d**)], the C-1 and C-3 chemical shifts predicted opposite stereochemistries, and therefore we felt unable to apply this analysis to any of our products.

‡ *Crystal data:* (**4b**), $C_{23}H_{24}N_2O_4$, monoclinic, space group $P2_1$, a = 10.312(5), b = 8.905(4), c = 11.330(5) Å, β = 100.9(1)°, U = 1022 Å^3, Z = 2, M = 392.5, D_c = 1.28 g cm^{-3}; (**3e**), $C_{18}H_{20}N_2O_6$, orthorhombic, space group $P2_12_12_1$, a = 13.809(6), b = 10.696(5), c = 12.056 Å, U = 1781 Å^3, Z = 4, M = 360.4, D_c = 1.34 g cm^{-3}. Data for both compounds were measured on a Hilger and Watts diffractometer with Cu-K_α radiation, and using ω—2θ scans with θ ≤55°. Both structures were solved by direct methods and refined anisotropically to give R values of 10.1 for (**4b**) (1133 independent observed reflections) and 8.7 for (**3e**) (1077 independent observed reflections). The molecular geometries of (**4b**) and (**3e**) corresponded closely to that observed for *trans*-1-ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline,[5] with the CO_2Me group attached to C-3 occupying an equatorial position in all three cases. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

benzyl derivative (**3f**); consequently, the stereochemistry of (**4f**), which was the C(1)-epimer of (**3f**), was established as being (1*R*),(3*S*). The stereochemistries of the other tetrahydro-β-carbolines were determined by carrying out the modifications of (**4b**) and (**4f**) outlined in Scheme 2; this allowed all of the peaks in the ^{13}C n.m.r. spectra to be unambiguously assigned to either the (1*S*),(3*S*)-(**3a—g**) or the (1*R*),(3*S*)-(**4a—g**) diastereoisomers, even in cases where these isomers could not be separated.

It was therefore possible to analyse fully the results of the addition–cyclisation reactions, and these are summarised in Table 1. It would seem that this modified Pictet–Spengler reaction can indeed be extended to the preparation of 1,3-disubstituted tetrahydro-β-carbolines, although enamine formation is very slow between methyl propynoate and (*S*)-tryptophan methyl esters. Subsequent cyclisation of these enamines (**4a—d**) does show some stereoselectivity, in qualitative agreement with the stereochemical observations from other Pictet–Spengler reactions,[2] and this could be important in the synthesis of optically active heteroyohimbine alkaloids.[1]

We thank the S.E.R.C. for a studentship (to S. P. H.), and Dr. A. J. G. Crawshaw for advice concerning ^{13}C n.m.r. spectra.

Received, 5th July 1985; Com. 960

References

1 For example, G. Massiot and T. Mulamba, *J. Chem. Soc., Chem. Commun.*, 1983, 1147, and references 1—4 therein.
2 For example, D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, 1979, **44**, 535, and references 4—7 therein.
3 J. Vercauteren, C. Lavaud, J. Lévy, and G. Massiot, *J. Org. Chem.*, 1984, **49**, 2278.
4 R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.
5 F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, 1980, **102**, 6976.
6 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
7 R. Z. Andriamialisoa, M. Langlois, and Y. Langlois, *J. Org. Chem.*, 1985, **50**, 961.