Pergamon

Tetrahedron Letters 41 (2000) 4977–4980

TETRAHEDRON LETTERS

Pictet–Spengler reaction: is carbonyl the best choice? A highly diastereoselective alternative approach to *trans*-1,3-disubstituted tetrahydro-β-carbolines

Kamaljit Singh* and Prasant K. Deb

Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar 143 005, India

Received 7 March 2000; accepted 8 May 2000

Abstract

Unprecedented 1,2,3-trisubstituted tetrahydro-β-carbolines (THBCs) have been synthesized via a short and highly diastereoselective synthetic route. The key step of the sequence is a flexible variant of the Pictet–Spengler reaction employing synthetic equivalents of several non-available carbonyl compounds. Using one such synthon, the resultant THBC could be further ring-closed to a tetracyclic indole alkaloidal skeleton.

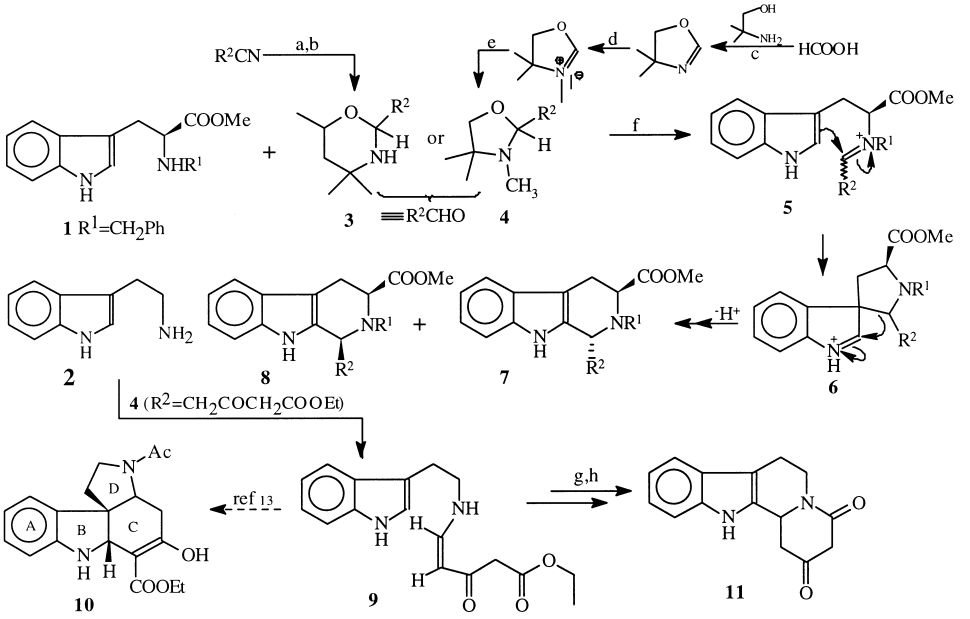
The Pictet–Spengler reaction[1] has proved to be a tool of importance in the synthesis of tetrahydro-β-carbolines (THBCs) and related heterocyclic systems. With the advent of asymmetric stereocontrol,[2] the importance of this method for the stereospecific synthesis of the THBC core has rapidly increased culminating in enantioselective and diastereoselective preparations of this type of compound using carbohydrates,[3] (*R*)- and (*S*)-glyceraldehyde,[4] (–)-8-phenylmethylcarbamates,[5] chiral acetylenic sulphoxides,[6] chemoselective and asymmetric reductions,[7] etc. A salient feature of these reactions has been the diversification at C-1, an attribute of potential utility in the total syntheses of indole alkaloids and lead compounds showing a variety of pharmacologically interesting properties. With the major emphasis laid on the stereocontrol of the reaction using relatively stable aromatic aldehydes, the prime limitations of the conventional Pictet–Spengler condensation include the use of rather inaccessible functionalized aliphatic aldehydes and, although widely realized,[8] have not been adequately addressed. Even under non-acidic aprotic conditions, with an excess of aldehyde (10–15 equivalents) to compensate for competitive side reactions,[8b] (including aldol condensation of the aldehydes to give α,β-unsaturated carbonyl compounds and their instability), lower yields and the presence of unreacted starting materials plague the reaction. In keeping with our interest in a more general route to the C-1 diversified title

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00751-6

compounds and in the light of the above, we wished to add a new dimension to their thermodynamically controlled, high yielding and diastereoselective synthesis by employing readily available perhydro-1,3-heterocycles: oxazines **3** and oxazolidines **4** (carbonyl equivalents),[9] capable of transferring multi-functionalized carbon (C-2) fragments to biogenic amines, resulting in variously C-1-substituted THBCs.

The oxazines **3** ($R^2 = CH_3$, C_2H_5, CH_2COOEt, CH_2CH_2SEt/Ph) used as reagents are readily available from a variety of cheaply available starting materials employing literature[10a] or modified[10b] methods. Another approach that has been developed[10c] involves reacting 2-chloromethyl dihydro-oxazine (obtained from chloroacetonitrile) with the carbanion of acetonitrile generated at low temperature (LDA, THF, –78°C) followed by reduction ($NaBH_4$, THF:EtOH (1:1), –40°C) to give **3** ($R^2 = CH_2CH_2CN$). Likewise, oxazolidines **4** ($R^2 = CH_2CN$, CH_2COCH_2COOEt, $CH_2COC_6H_5$) have also been synthesized by reacting carbanions of acetonitrile, ethyl acetoacetate and acetophenone (LDA/THF/–78°C) with 2,4,4-trimethyl-Δ^2-oxazolinium iodide[11] (Scheme 1).



Scheme 1. (a) Ritter synthesis of dihydro-oxazine: 2-methyl-2,4-pentanediol, 0°C, quantitative; (b) reduction: $NaBH_4$, THF:EtOH (1:1), –40°C, quantitative; (c) oxazoline synthesis: reflux, 80%; (d) N-quaternisation: MeI, quantitative; (e) carbanion addition, THF, –78°C; (f) MeCN: acid 10:1, 80°C; (g) EtOH/HCl, quantitative; (h) aq. NH_3, 80%

If a stoichiometric mixture of N_b-benzyl (L)-tryptophan methyl ester (TrypOMe) **1** in anhydrous acetonitrile:acid (10:1) solution (Table 1) is reacted under reflux with oxazines **3** (existing mainly in their enamine-chain tautomeric form)[11] or oxazolidines **4** (existing as ring-chain tautomers)[12] the iminium intermediate **5** (Scheme 1) formed in situ cyclizes spontaneously by intramolecular electrophilic attack of the iminium carbon at C-2 or at C-3 of the indole moiety to form a spiroindolenine[1,2b] **6** which rearranges and deprotonates to yield THBCs **7** and **8** in high yield and very high diastereomeric ratios (Table 1). The *trans*- N_b-substituted diastereomers are thermodynamically more stable than their *cis*-congeners. Evidence for this observation has already been furnished and proved by equilibration in acidic media.[1]

Table 1
Diastereoselectivity in the Pictet–Spengler reaction between oxazines **3** or oxazolidines **4** and N_b benzyl (L)-TrypOMe **1**

Entry	R^2	Acid	Reagent 3/4	Diastereomeric ratio[a] 7	8	Isolated yield (%)	Reaction time (h)
1.	CH_3	TFA	**3**	87	13	80	8
2.	CH_2CH_3	TFA	**3**	88	12	74	24
3.	CH_2CN	AcOH	**4**	88	12	78	12
4.	CH_2CH_2CN	TFA	**3**	93	7	61	30
5.	CH_2COOEt	TFA	**3**	93	7	86	24
6.[b]	CH_2COCH_2COOEt	AcOH	**4**	96	4	56	40
7.[c]	$CH_2COC_6H_5$	TFA	**4**	95	5	54	36
8.	CH_2CH_2SEt	AcOH	**3**	92	8	78	24
9.	CH_2CH_2SPh	AcOH	**3**	95	5	72	12

[a] ± 3% As determined by integration of the ^1H NMR peaks; [b]obtained from **9** (benzene/HCl); [c]obtained from the corresponding enaminoketone (corresponding to **9**).

In all the examples recorded herein, the use of sensitive aldehydes[8] is avoided. This synthesis is particularly attractive in light of the large number of commercially available precursors of oxazines **3** and oxazolidines **4** and can be used to introduce much needed diversity at the C-1 position of the THBCs.

The structures of all compounds were supported by 300 MHz ^1H and 50.3 MHz ^{13}C NMR and mass spectra. All compounds give a single spot on TLC analysis and correct microanalytical data. Spin decouplings (entry **9**) and 2D NMR spectra (entry **8**) are used to assign signals in the ^1H NMR spectra. The diastereomers are identified by ^1H and ^{13}C NMR and the stereochemistry was unambiguously assigned by comparison with literature data.[14] Due to space restrictions only salient chemical shifts in the NMR are presented.[15]

2,4-Dioxo-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-*a*] quinolizine **11** (a ketolactam) is a compound of interest in connection with the total synthesis of indole alkaloids and their analogs. The known synthesis[16] of **11** proceeds in low yield and requires the use of sensitive 4-ethoxycarbonyl–3,3-ethylenedioxybutanal. The reaction of tryptamine **2** with **4** ($R^2 = CH_2COCH_2COOEt$) (anhydrous CH_3CN:CH_3COOH, 10:1, reflux) furnished enaminoketone ester **9**[17] and this was converted into **11** (Scheme 1) in 80% yield. Likewise, the dihydroindole **10** (a potential vindoline)[13] intermediate, has been obtained by acetylation of the amine **9** and treatment of the resultant acetyl derivative with BF_3/Et_2O to obtain **10**.[13]

Entry **3** constitutes straightforward incorporation of the $-CH_2CN$ functionality at C-1, to furnish an analog of a pivotal intermediate used in the synthesis of corynantheidol and dihydrocorynantheol and related *seco*-alkaloids, otherwise prepared through a cumbersome, multistep approach.[18]

In summary, several oxazines **3** and oxazolidines **4**, synthetic equivalents of aldehydes, have been synthesized and used in the Pictet–Spengler reaction with TrypOMe and tryptamine to give C-1-functionalized THBCs in excellent yields and very high diastereoselectivity. This protocol is flexible for many variations at C-1. The application of the methodology in the synthesis of some isoquinoline alkaloidal skeletons is in progress.

Acknowledgements

We wish to thank CSIR, New Delhi for the grant [01 (1441)/97-EMR-II], senior research fellowship to P.K.D. and Professor Harjit Singh, Department of Chemistry for helpful suggestions.

References

1. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797, and references cited therein.
2. (a) Czerwinski, K. M.; Cook, J. M. *Stereochemical Control of the Pictet–Spengler Reaction in the Synthesis of Natural Product Synthesis*; Pearson, W., Ed.; JAI Press: Greenwich, CT, 1996; Vol 3, p. 217. (b) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* 1993, 431.
3. Piper, I. M.; MacLean, D. B.; Kvarnstrom, I.; Szarek, W. A. *Can. J. Chem.* **1983**, *61*, 2721.
4. Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Can. J. Chem.* **1986**, *64*, 2205.
5. Bauer, T.; Chapuis, C.; Kozak, J.; Jurezak, J. *Helv. Chim. Acta.* **1989**, *72*, 482.
6. Lee, A. W. M.; Chan, W. H. *Chiral Acetylenic Sulfoxides and Related Compounds in Organic Synthesis in Topics in Current Chemistry*; Springer-Verlag, 1997; Vol. 190, p. 103.
7. McNulty, J.; Still, I. W. J. *Tetrahedron Lett.* **1995**, 36, 7965.
8. (a) Gremmen, C.; Burm, B. E. A.; Wenner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 1441. (b) Ungemach, F.; DiPiero, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164. (c) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Everett, J. H.; Reynolds, C. D.; Stephen, D. W.; Giordano, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 451. (d) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, 62, 44. [Entry 1: obtained as mixture (*trans*:*cis*, 77:23) after a 72 h reaction in a sealed tube].
9. Singh, K.; Deb, P. K. *Heterocycles* **1999**, *51*, 1509.
10. (a) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36. (b) Singh, K.; Singh, J.; Deb, P. K.; Singh, H. *Tetrahedron* **1999**, *55*, 12873. (c) Singh, K.; Deb, P. K. Unpublished.
11. Singh, K.; Singh, J.; Singh, H. *Tetrahedron* **1998**, *54*, 3567.
12. Lazar, L.; Lakatos, A. G.; Fulop, F.; Bernath, G.; Riddell, F. G. *Tetrahedron* **1997**, *53*, 1081.
13. Hiemstra, H. C.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1982**, *23*, 3301.
14. (a) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976. (b) Bailey, P. D.; Hollinshead, S. P. *Heterocycles 1987*, *26*, 389.
15. Entry 3 (*cis*-isomer): ^{1}H NMR ($CDCl_3$): δ 2.82–3.50 (m, 4H, 2×CH_2), 3.65 (s, 3H, OCH_3), 3.95 (dd, $J_1 = 6.87$ Hz and $J_2 = 2.07$ Hz, 1H, CH), 4.17 (s, 2H, CH_2), 4.50 (dd, $J_1 = 8.50$ Hz and $J_2 = 2.92$ Hz, 1H, CH), 7.11–7.23 Hz (m, 2H, arom H), 7.31–7.43 (m, 6H, arom H), 7.54 (d, $J = 7.31$ Hz, 1H arom H), 8.28 (br, 1H, NH). Entry 3 (*trans*-isomer): ^{1}H NMR ($CDCl_3$): δ 2.67–2.91 (ABX system, $J_{AB} = 16.68$ Hz, $J_{AX} = 4.92$ Hz, $J_{BX} = 7.89$ Hz, 2H, CH_2), 3.04–3.25 (m, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.85 (AB quartet, $J = 14.42$ Hz, 2H, CH_2), 3.91–3.97 (m, 1H, CH), 4.44 (dd, $J_1 = 7.59$ Hz and $J_2 = 5.12$ Hz, 1H, CH), 7.09–7.31 (m, 2H, arom H), 7.33–7.42 (m, 6H, arom H), 7.53 (d, $J = 7.72$ Hz, 1H, arom H), 8.05 (br, 1H, NH).
16. Brutcher Jr., F. V.; Vanderwerff, W. D. *J. Org. Chem.* **1972**, *37*, 297.
17. The *Z*-configuration of **9** was attested by the coupling constants of the vinylic protons (δ 4.93, $J = 7.2$ Hz).
18. Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091.