Tetrahedron Letters 54 (2013) 3801–3804

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple entry to sugar derived bispiropyrrolidines through non-stabilized azomethine ylides

Piyali Deb Barman, Divya Goyal, Upendra Kumar Daravath, Ishita Sanyal, Sukhendu B. Mandal, Asish Kumar Banerjee *

Department of Chemistry, CSIR-Indian Institute of Chemical Biology, 4 Raja S.C. Mullick Road, Jadavpur, Kolkata 700 032, India

ARTICLE INFO

Article history:
Received 5 March 2013
Revised 6 May 2013
Accepted 9 May 2013
Available online 15 May 2013

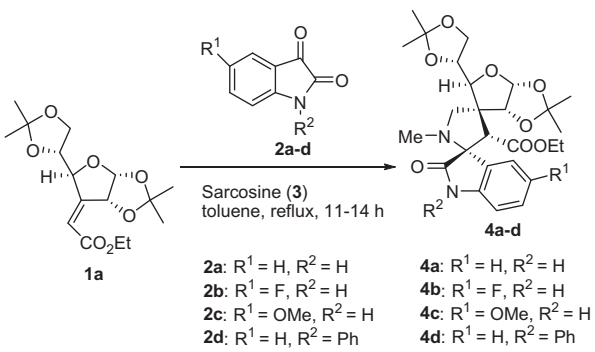
Keywords:
Heterocycles
Bispiropyrrolidines
Carbohydrates
Azomethine ylides
Cycloaddition reactions

ABSTRACT

1,3-Dipolar cycloaddition reaction of a carbohydrate-derived exocyclic olefin with in situ generated non-stabilized azomethine ylides, formed by the reaction of sarcosine (a secondary α-amino acid) with isatins, acenaphthenedione and cycloalkanones in refluxing toluene afforded bispiropyrrolidine derivatives in 78–92% yield, when DIPEA was used as a base. However, using Et_3N/DBU, the reaction of the olefin precursor with azomethine ylide (derived from the condensation of cyclopentanone and sarcosine) furnished the product in 51–53% yield. On the other hand, in the absence of a base the yield of the cycloaddition product was dramatically decreased to 10–22%.

Recent research has witnessed a rising demand on the development of unique and diversified structural motifs due to their presence in many bioactive natural and synthetic molecules[1] that have potential usefulness as drugs for the treatment of antitumor,[2] HINI influenza,[3] HIV,[4] cancer[5] etc. Some bioactive naturally occurring alkaloids, viz. rhynchophylline,[6a] formsamine,[6b] horsfiline,[6c] elacomine,[6d] spirotryprostatin A & B[6e,f] contain monospiropyrrolidinyl-oxindole moiety and are reported to have numerous biological activities including antitumor activity against various cell lines, inhibitory activity against microtubule assembly and mammalian cell cycles, and modification of function of muscarinic serotonin receptors. Synthesis of these scaffolds and several spirooxindole analogues exhibiting inhibitory activities against poliovirus/rhinovirus 3C-proteinase and aldose reductase have been realized by utilizing the well known 1,3-dipolar azomethine ylide cycloaddition reaction.[7–9] Even sugar-based spiropyrrolidinyl-oxindoles have recently been synthesized utilizing this key step.[10] The presence of bispiropyrrolidinyl-oxindole scaffolds in natural products, to the best of our knowledge, is hitherto unknown in the literature. Nevertheless, they have received a great deal of attention among synthetic chemists due to their immense activity[11] against diabetes, bacteria, fungi, microbes and mycobacteria. A numerous reports[12] for the synthesis of bispiropyrrolo-/pyrrolizino-/pyrrolothiazolo-oxindoles by addition of azomethine ylides to a variety of non-sugar-based olefins have been documented. However, much synthetic research work on sugar-based bispiro compounds has not been initiated.

We, therefore, envisioned that hybridizing bispiropyrrolidinyl-oxindole decoration with sugar derived precursors involving azomethine ylides could lead to the discovery of a unique class of carbohydrate-derived bispiro heterocycles of potential biological significance. To this end, we now report an expeditious approach to target a new kind of sugar-fused bispiropyrrolidinyl-oxindoles/-acenaphthylenone/-cycloalkane derivatives using a secondary α-amino acid (sarcosine), 1,2-diketones (isatin and acenaphthoquinone), cycloalkanones and the sugar-derived olefin precursor.



Scheme 1. Synthesis of sugar-based bispiroheterocycles via azomethine ylides.

* Corresponding author. Tel.: +91 33 2429 2422; fax: +91 33 2473 5197.
E-mail address: ashisbanerjee@iicb.res.in (A.K. Banerjee).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.027

In our initial attempt (Scheme 1), reaction of the sugar-derived exocyclic olefin, the required dipolarophile **1a** with the non-stabilized azomethine ylide, generated in situ by the condensation of isatin **2a** with the amino acid sarcosine (**3**) in toluene at reflux temperature for 12 h furnished the bispiropyrrolidinyl-oxindole derivative **4a** in 83% yield. Similar reactions of the substituted isatins **2b–d** afforded **4b–d** in 78%, 85% and 81% yields, respectively. The structure of **4a–d**[13,14] was elucidated from the ^{1}H and ^{13}C NMR spectroscopic data. The formation of the pyrrolidine moiety in **4a** was confirmed by the appearance of three-proton singlet (NCH_3) at δ 2.21 and two-proton singlet (NCH_2) at δ 3.43 in the ^{1}H NMR spectrum. The observed singlet at δ 3.97 was assigned for the $CHCO_2Et$ in the pyrrolidine moiety. The presence of the signals at δ 55.0 (CH), 56.2 (CH_2), 57.4 (C) and 73.1 (C) in the ^{13}C NMR spectrum also indicated the creation of the pyrrolidine ring during the cycloaddition reaction. Finally, the structural confirmation of **4a** was obtained from a single crystal X-ray crystallographic study (the ORTEP diagram is given in Fig. 1).[15]

We next turned our attention to generalize the methodology employing non-aromatic cycloalkanones, instead of isatins, for the generation of azomethine ylide (1,3-dipoles) by the reaction with sarcosine, although a very few reports exist in the literature on this method.[16] Thus, at the outset, we chose cyclopentanone (**5a**) and sarcosine (**3**) as the ylide generator and reacted with **1a** (Scheme 2) under the previously optimized reaction condition. This although produced the desired product **6a**,[13] the yield was too low (22% Table 1). A careful modification of the reaction condition was, therefore, needed.

We first decided to screen solvents of the reaction. Attempts employing methanol, *o*-xylene, DMF, DMSO etc. under the conventional solution-phase protocols were frustrating, yielding product **6a** to the extent of 10–22% (entries 1–5). Thus, in a modified approach, the addition of Et_3N into the reaction mixture to facilitate the decarboxylation of sarcosine-iminium ion[9b] in forming an ylide improved the yield up to 51% (entry 6). The coupling was then further reinvestigated by replacing Et_3N by DBU. This, however, failed to show any substantial improvement in the outcome (Table 1, entry 7) and had to be discarded. Finally, we tested DIPEA as the base to condense **1a** with **5a**, which led to maximization of the product yield (92%) in 10 h under reflux condition in toluene (entry 8).[17]

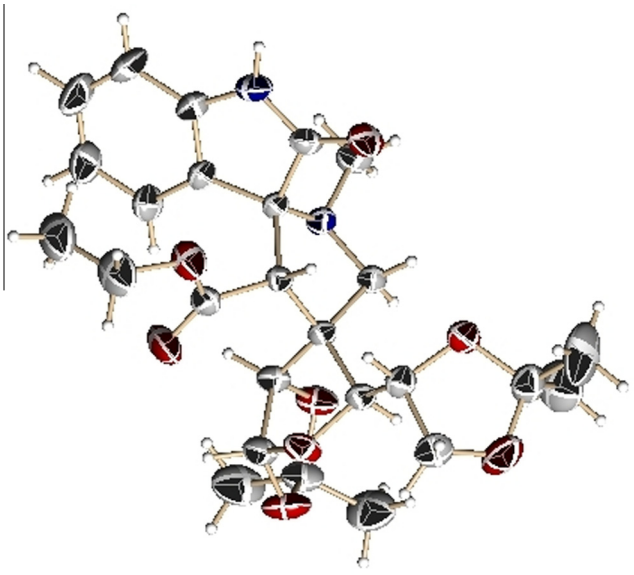
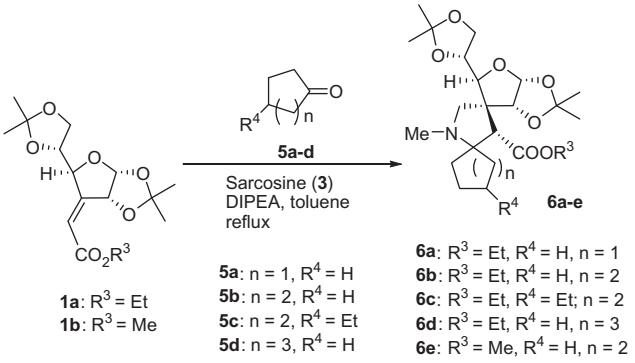


Figure 1. ORTEP diagram of **4a**. The displacement ellipsoids are drawn at the probability of 50%.



Scheme 2. Synthesis of sugar-fused bispiroheterocycles using cycloalkanones.

Table 1
Optimization of reaction condition between **1a** and **5a**

Entry	Base	Solvent	Time (h)	Temp (°C)	Yield[a] (%)
1	None	Toluene	10	Reflux	22
2	None	Methanol	10	Reflux	10
3	None	*o*-Xylene	12	120	20
4	None	DMF	12	130	14
5	None	DMSO	12	130	12
6	Et_3N	Toluene	10	Reflux	51
7	DBU	Toluene	10	Reflux	53
8	DIPEA	Toluene	10	Reflux	92

[a] Isolated yield.

The success of the above cycloaddition reaction with cyclopentanone prompted us to test this newly developed reaction tool in other higher homologues of cycloalkanones (Scheme 2). Thus, cyclohexanones (**5b**,**c**) and cycloheptanone (**5d**) were reacted with the dipolarophiles (**1a**,**b**) under the optimal set of reaction conditions, producing the corresponding cycloadducts (**6b–e**)[12] in high yields (Table 2, entries 2–5). The structures of all the bispiropyrrolidinyl-cycloalkanes were confirmed by NMR analyses. They also exhibited exact masses in their mass spectra.

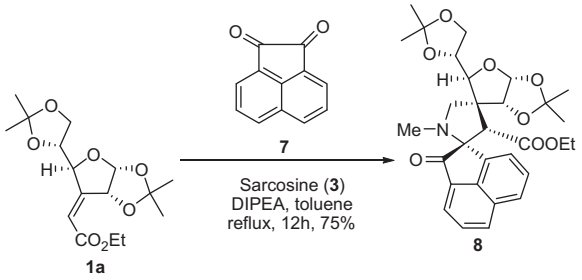
Once these bispiropyrrolidines with cycloalkane rings were constructed, we moved towards attempting the synthesis of analogous bispiropyrrolidine using sterically hindered ketone acenaphthoquinone **7**, which also led to the cycloadduct **8** (Scheme 3) in 75% yield upon reaction with the azomethine ylide, generated from **7** and **3**, the structure of which was deduced by spectral analyses.

From mechanistic considerations, the cycloaddition reaction, we believe, proceeds with an initial iminium ion formation, which subsequently decarboxylates (facilitated by DIPEA) to generate an ylide (1,3-dipole) (Fig. 2). Once the ylide is formed, it behaves as a nucleophile and attacks the dipolarophile **1a**/**1b** to produce the cycloadducts in high yields upon [3+2] cycloaddition reaction. It is worthy to mention that the cycloadducts were essentially

Table 2
Synthesis of sugar-fused bispiroheterocycles using cycloalkanones **5a–d**[a]

Entry	Dipolarophile	Ketone	Time (h)	Product	Yield[b] (%)
1	**1a**	**5a**	10	**6a**	92
2	**1a**	**5b**	14	**6b**	88
3	**1a**	**5c**	11	**6c**	85
4	**1a**	**5d**	11	**6d**	82
5	**1b**	**5b**	14	**6e**	78

[a] All the reactions were performed in toluene under reflux condition using sarcosine and DIPEA as the base.
[b] Isolated yield.



Scheme 3. Synthesis of bispiroheterocycles using acenaphthaquinone.

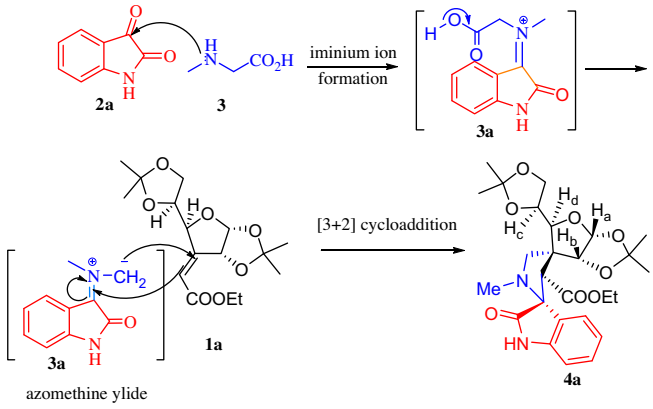


Figure 2. Mechanistic pathway for the formation of bispiroheterocycles.

formed by the attack of the dipole from the face opposite to the tangled isopropylidene moiety in order to avoid a higher steric crowding. This leads to the projection of the ester moiety towards β-face. Furthermore, it is also expected that, in order to wipe out the possibility of dipolar repulsion between amide carbonyl and ester carbonyl groups, the amide group of isatin should be placed in the plane opposite to the ester moiety. This proposition was indeed reflected in the reaction of the olefin **1a** with azomethine ylide **3a** affording the cycloadduct **4a**. The structure of **4a** was confirmed by single crystal X-ray analysis.

In conclusion, three-component 1,3-dipolar azomethine cycloaddition reactions to synthesize bispiropyrrolidines containing oxindoles, cycloalkanes and cycloalkanone in excellent yields in an optimized reaction condition have been successfully demonstrated. This strategy provides opportunities for the preparation of libraries of carbohydrate-based bispiropyrrolidine hybrid molecules for biological screening.

Acknowledgements

The authors gratefully acknowledge the Council of Scientific and Industrial Research for providing Senior Research Fellowships (to P.D.B. and I.S.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.027.

References and notes

1. (a) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878–2890. and references cited therein; (b) Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 8201–8203; (c) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199–3202.
2. Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1994**, *35*, 4591–4594.
3. Ferguson, N. M.; Cummings, D. A. T.; Cauchemez, S.; Fraser, C.; Riley, S.; Meeyai, A.; Iamsirithaworn, S.; Burke, D. S. *Nature* **2005**, *437*, 209–214.
4. Kim, H. O.; Ahn, S. K.; Alves, A. J.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; Roey, P. V.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1992**, *35*, 1987–1995.
5. (a) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863; (b) Allen, J. R.; Harris, C. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1890–1897.
6. (a) Chou, C. H.; Gong, C. L.; Chao, C. C.; Lin, C. H.; Kwan, C. Y.; Hsieh, C. L.; Leung, Y. M. *J. Nat. Prod.* **2009**, *72*, 830–834; (b) Beecham, A. F.; Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Chem. Commun.* **1967**, 535–536; (c) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527–6530; (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711–713; (e) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 4249–4251; (f) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2007**, *9*, 2763–2766.
7. (a) Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277–7280; (b) Cravotto, G.; Giovenzani, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447–8453; (c) Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175–9178; (d) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667; (e) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311–6322.
8. (a) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180–181; (b) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182–183; (c) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703–2713.
9. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809.
10. (a) Prasanna, R.; Purushothaman, S.; Raghunathan, R. *Tetrahedron Lett.* **2010**, *51*, 4538–4542; (b) Barman, P. D.; Sanyal, I.; Mandal, S. B.; Banerjee, A. K. *Synthesis* **2011**, *21*, 3563–3568.
11. (a) Murugan, R.; Anbazhagan, S.; Narayanan, S. S. *Eur. J. Med. Chem.* **2009**, *44*, 3272–3279; (b) Karthikeyan, K.; Sivakumar, P. M.; Doble, M.; Perumal, P. T. *Eur. J. Med. Chem.* **2010**, *45*, 3446–3452; (c) Periyasami, G.; Raghunathan, R.; Surendiran, G.; Mathivanan, N. *Eur. J. Med. Chem.* **2009**, *44*, 959–966; (d) Wei, A. C.; Ali, M. A.; Yoon, Y. K.; Ismail, R.; Choon, T. S.; Kumar, R. S.; Arumugam, N.; Almansour, A. I.; Osman, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4930–4933.
12. (a) Bakthadoss, M. K.; Kannan, D.; Sivakumar, G. *Synthesis* **2012**, *44*, 793–799; (b) Lakshmi, N. V.; Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 1064–1068; (c) Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4618–4620; (d) Lashgari, N.; Ziarani, G. M. *ARKIVOC* **2012**, *i*, 277–320. and references cited therein; (e) Liu, J.; Sun, H.; Liu, X.; Ouyang, L.; Xie, Y.; Wang, X. *Tetrahedron Lett.* **2012**, *53*, 2336–2340; (f) Raj, A. A.; Raghunathan, R.; Sridevikumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407–419; (g) Velikorodov, A. V.; Poddubnyi, O. Y.; Krivosheev, O. O.; Titova, O. L. *Russ. J. Org. Chem.* **2011**, *47*, 402.
13. *General procedure for the synthesis of glycobispiro heterocycles* ***4a–d***, ***6a–e*** *and* ***8***: A mixture of the carbohydrate-derived olefin **1a** (0.25 mmol, 1.0 equiv), isatins **2a–d** (0.275 mmol, 1.1 equiv), sarcosine **3** (0.275 mmol, 1.1 equiv), was heated at reflux in toluene (10 mL) under N_2 for 11–14 h. The reaction mixture was cooled and the solvent was evaporated under reduced pressure to a residue, which was purified by column chromatography on silica gel (100–200 mesh) using EtOAc/petroleum ether (1:4) as eluent to furnish **4a–d**. The compounds **6a–e** and **8** were similarly synthesized using **1a**/**b** (0.25 mmol, 1.0 equiv), **5a–d**/**7** (0.275 mmol, 1.1 equiv), 3 (0.275 mmol, 1.1 equiv) and diisopropyl ethylamine (DIPEA) (0.25 mmol, 1.0 equiv) followed by purification by chromatography.
Spectral data of ***4a***: Light yellow solid; mp 230 °C; $[\alpha]_D^{25}$ −69.4 (*c* 0.6, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 0.66 (t, 3H, *J* = 7.2 Hz), 1.41 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.57 (s, 3H), 2.21 (s, 3H), 3.43 (s, 2H), 3.62–3.65 (m, 2H), 3.97 (s, 1H), 3.98–4.01 (m, 2 H), 4.11–4.14 (m, 2H), 5.48 (d, 1H, *J* = 3.6 Hz), 6.05 (d, 1H, *J* = 4.2 Hz), 6.79 (d, 1H, *J* = 7.8 Hz), 7.05 (dt, *J* = 0.6, 1H, 7.8 Hz), 7.23 (dt, 1H, *J* = 1.2, 7.8 Hz), 7.32 (d, *J* = 7.2 Hz, 1H), 7.49 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.3 (CH_3), 25.4 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 35.1 (CH_3), 55.0 (CH), 56.2 (CH_2), 57.4 (C), 60.6 (CH_2), 68.0 (CH_2), 73.1 (C), 74.5 (CH), 79.4 (CH), 83.2 (CH), 105.9 (CH), 109.2 (C), 109.8 (CH), 111.0 (C), 122.9 (CH), 126.4 (CH), 128.2 (C), 129.5 (CH), 141.5 (C), 169.5 (C), 78.9 (C). HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_8$: 503.2388; found: 503.2408.
6a: Sticky light yellow liquid; $[\alpha]_D^{25}$ −90.4 (*c* 0.56, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.33 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.49 (s, 3H), 1.53–1.69 (m, 6H), 1.93–1.97 (m, 2H), 2.28 (s, 3H), 2.85 (d, 1H, *J* = 9.6 Hz), 3.05 (br s, 2H), 3.87 (d, 1H, *J* = 7.8 Hz), 3.97 (dd, 1H, *J* = 5.1, 8.4 Hz), 4.06–4.23 (m, 4H), 5.23 (d, 1H, *J* = 3.6 Hz), 5.61 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 24.5 (CH_2), 25.1 (CH_2), 25.3 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 26.7 (CH_3), 29.3 (CH_2), 34.4 (CH_2), 35.0 (CH_3), 55.2 (CH), 56.3 (CH_2), 56.9 (C), 60.6 (CH_2), 67.8 (CH_2), 74.0 (CH), 74.3 (C), 80.4 (CH), 82.9 (CH), 104.6 (CH), 109.4 (C), 110.7 (C), 172.0 (C). HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{37}NNaO_7$: 462.2462; found: 462.2480. **8**: sticky brown liquid; $[\alpha]_D^{25}$ −153.8 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 3.6 Hz), 1.47 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 1.62 (s, 3H), 2.14 (s, 3H), 3.27–3.33 (m, 2H), 3.55 (s, 2H), 4.02–4.19 (m, 5H), 5.65 (d, 1H, *J* = 3.9 Hz), 6.12 (d, 1H, *J* = 3.9 Hz), 7.68 (apparent d, 1H, *J* = 3.9 Hz), 7.75 (t, 2H, *J* = 7.5 Hz), 7.83–7.90 (m, 2H), 7.95 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.5 (CH_3), 25.4 (CH_3), 26.6 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 35.4 (CH_3), 55.1 (CH), 57.3 (C), 57.4 (CH_2), 60.1 (CH_2), 68.1 (CH_2), 74.5 (CH), 79.7 (CH), 83.3 (CH), 106.1 (CH), 109.8

(C), 111.0 (C), 118.9 (C), 121.1 (CH), 122.1 (CH), 128.5 (2 × CH), 130.2 (C), 131.0 (C), 132.6 (CH), 135.3 (CH), 143.0 (C), 169.8 (C), 207.1 (C), one C is not discernible. HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{30}H_{35}NNaO_8$: 560.2255; found: 560.2258.

14. Characterization data of **4b–d** and **6b–e** and copies of ^{1}H and ^{13}C NMR of all new compounds are given in the Supplementary data.
15. Crystallographic data of **4a** reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-926342. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/deposit (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
16. Tsuji, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079–4089.
17. (a) Chandrasekhar, S.; Basu, D.; Sailu, M.; Kotamraju, S. *Tetrahedron Lett.* **2009**, *50*, 4882–4884; (b) The low nucleophilicity of DIPEA due to steric hindrance enabled its use as a strong base and proton sponge, and avoided secondary reaction, which, however, could possibly occur via nucleophilic attack of Et_3N and DBU on the olefinic carbon of iminium ion giving rise to low yield of the products.