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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4899–4902

Biorenewable and mercaptoacetylating building blocks in the Biginelli reaction: synthesis of thiosugar-annulated dihydropyrimidines

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Received 22 February 2007; revised 2 May 2007; accepted 10 May 2007
Available online 17 May 2007

Abstract—A novel version of the Biginelli reaction using an unprotected aldose as a biorenewable aldehyde component and 2-methyl-2-phenyl-1,3-oxathiolan-5-one as a mercaptoacetylating active methylene building block with urea/thiourea is reported. The reaction is nanoclay-catalysed, expeditious and effected under solvent-free microwave irradiation conditions in a one-pot procedure to yield diastereoselectively, thiosugar-annulated multifunctionalized dihydropyrimidines via intramolecular domino cyclocondensation reactions of an isolable intermediate.

In times where premium is put on speed, diversity and efficiency in modern drug discovery processes,[1,2] multicomponent reaction (MCR) strategies offer significant advantages over conventional linear-type syntheses.[3–7] One of the prominent MCRs is the venerable Biginelli reaction first reported in 1893[8] that produces the functionalized dihydropyrimidine (DHPM) scaffold representing a heterocyclic system of remarkable pharmacological efficiency. During the past decade, this long neglected MCR has experienced a noticeable revival, mainly due to the broad range of biological activities of DHPMs. For example, orally active antihypertensive agents[9–11] or α_{1a} adrenoceptor-selective antagonists.[12] Similarly, monastrol and various marine natural products incorporating DHPM scaffolds are valuable new leads for anticancer and AIDS therapy.[13,14]

In over 110 years of study of the Biginelli reaction, only minor structural variations in its three building blocks have been reported[15,16] apart from a very recently reported major structural variation where the urea component was replaced by a guanidine system.[17] However, to the best of our knowledge, there has been no such major structural variation in the active methylene building block, this could result in a novel version of the Biginelli reaction for the synthesis of multifunctionalized DHPMs. Herein, we report the first example of the Biginelli reaction employing 2-methyl-2-phenyl-1,3-oxathiolan-5-one, a recently reported[18] mercaptoacetylating agent **1** (Fig. 1) as a novel structural variant of the active methylene building block, with unprotected aldoses as a biorenewable aldehyde component. This is in accordance with 'renewable resources', a new and rapidly developing concept in the environmental and chemical sciences that concerns the wide use of biorenewable materials for industry.

We are aware of only a few reports dealing with the use of aldoses in the protected form to give DHPMs in the Biginelli reaction.[19,20] However, our work is essentially different from those reported as the use of unprotected aldoses would allow one-pot syntheses of hitherto unknown thiosugar-annulated DHPM scaffolds without tedious protection-deprotection protocols. Aside from the simple expectation that the presence of sugar

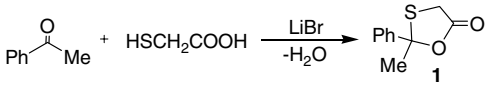

Figure 1. Formation of the mecaptoacetyl transfer agent 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1**.

Keywords: Biginelli reaction; Stereoselective synthesis; Dihydropyrimidines; Microwaves; 1,3-Oxathiolan-5-one; Solvent-free.
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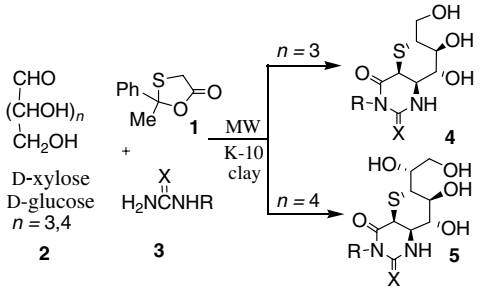
doi:10.1016/j.tetlet.2007.05.057

residues with free hydroxyl groups in the Biginelli products should increase the water solubility and bioavailability, other interesting biological properties may arise from the thiosugar-annulated DHPM system because thiosugars are potential targets for various carbohydrate-based therapeutics.[21] An additional reason for which we have been spurred to use aldoses in the Biginelli reaction stems from the desire to achieve a degree of internal asymmetric induction and thus obtain diastereomerically pure sugar-annulated DHPMs as the biological activity of DHPMs is strictly dependent on the absolute configuration at the C-4 stereocentre.[15,22] The present work is an outcome of our interest in devising new one-pot, solvent-free cyclization procedures,[18,23–26] especially involving stereocontrolled protocols.[18,25]

The strategy followed for the envisaged diastereoselective synthesis of thiosugar-annulated multifunctionalized dihydropyrimidines **4** and **5** consisted in microwave (MW) irradiation of an intimate solvent-free mixture of 2-methyl-2-phenyl-1,3-oxathiolan-5-one **1** with aldose **2**, urea/thiourea **3** and the nanoclay, Montmorillonite K-10 (particle size 32.7 nm), at 90 °C for 9–13 min in a CEM Discover Focussed Microwave Synthesis System (Scheme 1). Isolation and purification by recrystallisation from ethanol afforded **4** and **5** in 76–89% yields with >95% diastereoselectivity (Table 1) in favour of the cis isomer as determined by ^{1}H NMR spectroscopy.[27] In the cis isomers **4** and **5**, 4a-H is equatorial and 8a-H is axial as indicated by their coupling constants ($J_{4a,8a} = 4.9$ Hz, J_{cis} and $J_{8,8a} = 7.1$ Hz, J_{trans}). The crude isolates were checked by ^{1}H NMR for their diastereomeric ratios to note any inadvertent alteration of these ratios during subsequent purification. It was found that the use of other mineral catalysts, viz. silica gel, neutral or basic alumina, was far less effective, resulting in either no reaction (in the case of basic alumina) or relatively low yields (21–37%) of **4** and **5** (in the case of silica gel and neutral alumina). The formation of **4** and **5** may be tentatively rationalized by the conjugate addition of urea/thiourea **3** to adduct **6** generated in situ to afford intermediates, which undergo intramolecular domino cyclocondensation reactions to yield **4** and **5** (Scheme 2).



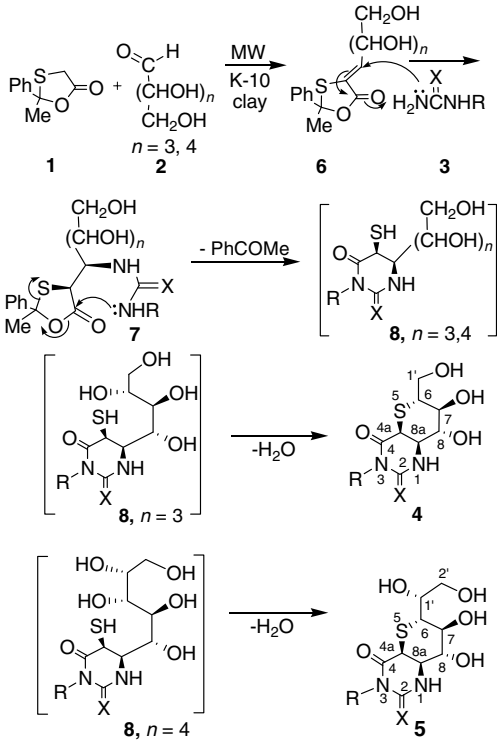
3-5	X	R	3-5	X	R
a	O	H	**d**	S	Ph
b	O	Ph	**e**	O	2-MeC$_6$H$_4$
c	S	H	**f**	O	Et

Scheme 1. Synthesis of thiosugar-annulated dihydropyrimidines **4** and **5**.

Table 1. Microwave-activated synthesis of **7**, **4** and **5**

Product	Time[a] (min)	Yield[b,c] (%)	cis:trans ratio[d]
7a	5	68	96:4
7i	7	79	98:2
4a	13	83	96:4
4b	10	76	97:3
4c	9	79	98:2
4d	12	85	96:4
4e	9	80	97:3
4f	10	82	96:4
5a	9	89	98:2
5b	11	78	97:3
5c	12	77	96:4
5d	10	84	96:4
5e	9	81	98:2
5f	11	80	97:3

[a] Microwave irradiation time at 90 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H and N analyses within ±0.34% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and FAB MS) data.
[d] As determined by ^{1}H NMR spectroscopy.



Scheme 2. Tentative mechanism for the intramolecular domino cyclocondensation reactions leading to dihydropyrimidines **4** and **5**.

It is noteworthy that acetophenone, which was used to activate mercaptoacetic acid to act as an efficient mercaptoacetylating active methylene building block **1**, was removed during the reaction yielding **4** and **5**. These conclusions are based on the observation that the representative intermediate compounds, **7a** ($n = 3$, X = O, R = H) and **7i** ($n = 4$, X = S, R = Ph), could be isolated in 68–79% yields with >95% cis diastereoselectivity, and that these could be converted into the corresponding thiosugar-annulated dihydropyrimidines **4a** and **5d**, respectively, in quantitative yields.[28]

In summary, we have developed a novel version of the Biginelli reaction using a mercaptoacetylating active methylene building block and an unprotected aldose as a biorenewable aldehyde component with urea/thiourea for the expeditious diastereoselective synthesis of thiosugar-annulated multifunctionalized dihydropyrimidine scaffolds of pharmacological potential. The reaction is nanoclay-catalyzed and performed under solvent-free MW irradiation conditions in a one-pot procedure.

Acknowledgements

We sincerely thank the DST, Govt. of India, for financial support, and SAIF, CDRI, Lucknow, for providing microanalyses and spectra.

References and notes

1. Plunkett, M.; Ellman, J. A. *Sci. Am.* **1997**, *276*, 68–73.
2. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
3. Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *18*, 115–122.
4. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.
5. Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363–371.
6. Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255–270.
7. Domling, A. *Comb. Chem. High Throughput Screening* **1998**, *1*, 1–22.
8. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–413.
9. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reily, B. C. *J. Med. Chem.* **1991**, *34*, 806–811.
10. Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reily, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254–3263.
11. Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289–294.
12. Barrow, J. C.; Nantermet, F. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703–2718.
13. (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971–974; (b) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. *Chem. Biol.* **2000**, *7*, 275–286.
14. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Trunech, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. N. *J. Org. Chem.* **1995**, *60*, 1182–1188.
15. Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888.
16. Dallinger, D.; Stadler, A.; Kappe, C. O. *Pure Appl. Chem.* **2004**, *76*, 1017–1024.
17. Nilson, B. L.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 7706–7714.
18. Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Tetrahedron* **2005**, *61*, 10013–10017.
19. Fernandez, M. V.; Herrera, F. J. L.; Cobos, T. L. *Heterocycles* **1988**, *27*, 2133–2140.
20. Fernandez, M. V.; Herrera, F. J. L.; Cobos, T. L. *Heterocycles* **1986**, *24*, 679–686.
21. Witczak, Z. J.; Culhane, J. M. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237–244.
22. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
23. Yadav, L. D. S.; Rai, V. K. *Tetrahedron Lett.* **2006**, *47*, 395–397.
24. Yadav, L. D. S.; Rai, V. K. *Tetrahedron* **2006**, *62*, 8029–8034.
25. Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Green Chem.* **2006**, *8*, 455–458.
26. Yadav, L. D. S.; Kapoor, R. *J. Org. Chem.* **2004**, *69*, 8118–8120.
27. General procedure for the synthesis of thiosugar-annulated dihydropyrimidines **4** and **5**: An intimate solvent-free mixture of 1,3-oxathiolan-5-one **1** (2.0 mmol), aldose **2** (2.0 mmol), urea/thiourea **3** (2.0 mmol) and Montmorillonite K-10 clay (0.20 g, particle size 32.7 nm) was taken in a 20 mL vial and subjected to MW irradiation for 9–13 min (Table 1). After completion of the reaction as indicated by TLC (hexane–AcOEt, 7:3, v/v), water (10 mL) was added to the reaction mixture with stirring for 10 min. The yellowish precipitate thus obtained was washed with water to give the crude product which was recrystallized from ethanol to afford a diastereomeric mixture (>95:<5; in the crude products, the ratio was >92:<8, as determined by ^{1}H NMR spectroscopy). The product on second recrystallization from ethanol furnished an analytically pure sample of a single diastereomer **4** or **5** (Table 1). On the basis of comparison of J values with literature values,[18,29–33] the cis stereochemistry was assigned to **4** and **5**, as the coupling constant ($J_{4a,8a}$ = 4.9 Hz) of the major cis diastereomer was lower than that for the minor trans diastereomer ($J_{4a,8a}$ = 10.1 Hz). Physical data of representative compounds: Compound **4a**: Pale yellow powder, mp 119–121 °C. IR (KBr) ν_{max} 3341, 3325, 3009, 1671, 1685, 1601, 1579, 1451 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): δ 3.31 (ddd, 1H, $J_{6,7}$ = 9.4 Hz, $J_{1'Ha,6}$ = 6.1 Hz, $J_{1'Hb,6}$ = 2.5 Hz, 6-H), 3.49 (dd, 1H, $J_{1Ha,1'Hb}$ = 12.0, $J_{1'Ha,6}$ = 6.1 Hz, 1′-H_a), 3.71 (dd, 1H, $J_{6,7}$ = 9.4 Hz, $J_{7,8}$ = 9.1 Hz, 7-H), 3.91 (dd, 1H, $J_{1'Ha,\ Hb}$ = 12.0 Hz, $J_{1'Hb,6}$ = 2.5 Hz, 1′-H_b), 4.09 (dd, 1H, $J_{7,8}$ = 9.1 Hz, $J_{8,8a}$ = 7.1 Hz, 8-H), 5.03 (dd, 1H, $J_{8,8a}$ = 7.1 Hz, $J_{4a,8a}$ = 4.9 Hz, 8a-H), 6.18 (d, 1H, $J_{4a,8a}$ = 4.9 Hz, 4a-H). ^{13}C NMR (DMSO-d_6): δ 25.3, 59.9, 69.3, 73.7, 74.5, 80.2, 165.9, 168.1. MS (FAB) m/z 249 (MH^+). Anal. Calcd for $C_8H_{12}N_2O_5S$: C, 38.70; H, 4.87; N, 11.28. Found: C, 38.53; H, 4.93; N, 11.51. Compound **4d**: Pale yellow powder, mp 135–137 °C. IR (KBr) ν_{max} 3338, 3328, 3011, 1681, 1605, 1577, 1453, 1097 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): δ 3.37 (ddd, 1H, $J_{6,7}$ = 9.4 Hz, $J_{1'Ha,6}$ = 6.2 Hz, $J_{1'Hb,6}$ = 2.7 Hz, 6-H), 3.51 (dd, 1H, $J_{1'Ha,1'Hb}$ = 12.0, $J_{1'Ha,6}$ = 6.2 Hz, 1′-H_a), 3.76 (dd, 1H, $J_{6,7}$ = 9.4 Hz, $J_{7,8}$ = 8.9 Hz, 7-H), 3.88 (dd, 1H, $J_{7,8}$ = 8.9 Hz, $J_{8,8a}$ = 7.1 Hz, 8-H), 4.11 (dd, 1H, $J_{7,8}$ = 8.9 Hz, $J_{8,8a}$ = 7.1 Hz, 8-H), 4.99 (dd, 1H, $J_{8,8a}$ = 7.1 Hz, $J_{4a,8a}$ = 4.9 Hz, 8a-H), 6.21 (d, 1H, $J_{4a,8a}$ = 4.9 Hz, 4a-H), 7.09–7.89 (m, 5H_{arom}). ^{13}C NMR (DMSO-d_6): δ 25.5, 60.2, 70.2, 73.7, 74.2, 80.5, 126.5, 127.8, 128.5, 130.3, 132.9, 165.8, 192.2. MS (FAB) m/z 341 (MH^+). Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: C, 49.40; H, 4.74; N, 8.23. Found: C, 49.31; H, 4.41; N, 8.09. Compound **5a**: Pale yellow powder, mp 126–129 °C. IR (KBr) ν_{max} 3337, 3323, 3012, 1673, 1688, 1601, 1581, 1455 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): δ 3.29 (ddd, 1H, $J_{1',6}$ = 6.0 Hz, $J_{1',2'Ha}$ = 5.8 Hz, $J_{1',2'Hb}$ = 2.5 Hz, 1′-H), 3.43 (dd, 1H, $J_{6,7}$ = 9.1 Hz, $J_{1'6}$ = 6.0 Hz, 6-H), 3.58 (dd, 1H,

$J_{2'Ha,Hb} = 11.9$ Hz, $J_{1',2'Ha} = 5.8$ Hz, 2′-H_a), 3.78 (dd, 1H, $J_{7,8} = 9.2$ Hz, $J_{6,7} = 9.1$ Hz, 7-H), 3.89 (dd, 1H, $J_{2'Ha,Hb} = 11.9$ Hz, $J_{1',2'Hb} = 2.5$ Hz, 2′-H_b), 4.21 (dd, 1H, $J_{7,8} = 9.2$ Hz, $J_{8,8a} = 7.1$ Hz, 8-H), 4.98 (dd, 1H, $J_{8,8a} = 7.1$ Hz, $J_{4a,8a} = 4.9$ Hz, 8a-H), 6.23 (d, 1H, $J_{4a,8a} = 4.9$ Hz, 4a-H). ^{13}C NMR (DMSO-d_6): δ 25.9, 61.2, 66.8, 70.5, 73.3, 74.2, 79.8, 165.7, 167.1. MS (FAB) m/z 279 (MH^+). Anal. Calcd for $C_9H_{14}N_2O_6S$: C, 38.84; H, 5.07; N, 10. Found: C, 38.59; H, 5.28; N, 9.79. Compound **5d**: Pale yellow powder, mp 103–105 °C. IR (KBr) ν_{max} 3340, 3321, 3010, 1683, 1599, 1585, 1451, 1102 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): δ 3.31 (ddd, 1H, $J_{1',6} = 5.9$ Hz, $J_{1',2'Ha} = 5.5$ Hz, $J_{1',2'Hb} = 2.5$ Hz, 1′-H), 3.45 (dd, 1H, $J_{6,7} = 8.9$ Hz, $J_{1'6} = 5.9$ Hz, 6-H), 3.55 (dd, 1H, $J_{2'Ha,Hb} = 11.9$ Hz, $J_{1',2'Ha} = 5.5$ Hz, 2′-H_a), 3.79 (dd, 1H, $J_{7,8} = 9.1$ Hz, $J_{6,7} = 8.9$, Hz, 7-H), 3.92 (dd, 1H, $J_{2'Ha,Hb} = 11.9$ Hz, $J_{1',2'Hb} = 2.5$ Hz, 2′-H_b), 4.18 (dd, 1H, $J_{7,8} = 9.1$ Hz, $J_{8,8a} = 7.1$ Hz, 8-H), 5.05 (dd, 1H, $J_{8,8a} = 7.1$ Hz, $J_{4a,8a} = 4.9$ Hz, 8a-H), 6.25 (d, 1H, $J_{4a,8a} = 4.9$ Hz, 4a-H), 7.11–7.77 (m, 5H_{arom}). ^{13}C NMR (DMSO-d_6): δ 26.2, 61.5, 67.0, 70.1, 73.5, 74.2, 79.6, 125.7, 127.1, 128.9, 130.3, 133.0, 166.3, 191.9. MS (FAB) m/z 371 (MH^+). Anal. Calcd for $C_{15}H_{18}N_2O_5S_2$: C, 48.63; H, 4.90; N, 7.56. Found: C, 48.93; H, 4.83; N, 7.73.

28. General procedure for the isolation of Michael adducts **7a** ($n = 3$, X = O, R = H) and **7i** ($n = 4$, X = S, R = Ph) and their conversion into the corresponding annulated products **4a** and **5d**: The procedure followed was the same as described above for the synthesis of **4** and **5**, except that the duration of MW irradiation in this case was 5–7 min instead of 9–13 min for **4** and **5**. Adducts **7** were recrystallized from ethanol to give a diastereomeric mixture (>95:<5; in the crude products the ratio was >93:<7, as determined by ^{1}H NMR spectroscopy) which was again recrystallized from ethanol to obtain an analytical sample of **7a** and **7i**. Adducts **7a** and **7i** were assigned the *syn* stereochemistry as their ^{1}H NMR spectra exhibited a smaller coupling constant $J_{NCH,SCH} = 4.5$ Hz than that of the minor (<4%) diastereomer (*anti*), $J_{NCH,SCH} = 9.8$ Hz.[18,29–33] Finely powdered intermediate compounds **7a** and **7i** were MW irradiated for 4–6 min in the same way as described for the synthesis of **4** and **5** to give the corresponding annulated products **4a** and **5d**, quantitatively. Physical data of representative compounds: Compound **7a**: Pale yellow powder, mp 111–113 °C. IR (KBr) ν_{max} 3150, 3007, 1775, 1678, 1605, 1583, 1450 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): δ 2.31 (s, 3H, Me), 4.03 (dd, 1H, $J_{1',2'} = 6.8$ Hz, $J_{1',NCH} = 5.5$ Hz, 1′-H), 4.17 (dd, 1H, $J_{4'Ha,Hb} = 10.2$ Hz, $J_{4'Hb,3'} = 5.3$ Hz, 4′-H_b), 4.42 (dd, 1H, $J_{1',2'} = 6.8$ Hz, $J_{2',3'} = 4.2$ Hz, 2′-H), 4.63 (ddd, 1H, $J_{3,4'Hb} = 5.3$ Hz, $J_{3,4'Ha} = 5.3$ Hz, $J_{2',3'} = 4.2$ Hz, 3′-H), 4.85 (dd, 1H, $J_{4'Ha,Hb} = 10.2$ Hz,$J_{3,4'Ha} = 5.3$ Hz, 4′-H_a), 5.01 (dd, 1H, $J_{1',NCH} = 5.5$ Hz, $J_{SCH,NCH} = 4.5$ Hz, NCH), 6.72 (d, 1H, $J_{SCH,NCH} = 4.5$ Hz, SCH), 7.05–7.67 (m, 5H_{arom}). ^{13}C NMR (DMSO-d_6): δ 20.5, 35.1, 64.7, 65.2, 70.1, 71.1, 72.0, 74.5, 127.2, 128.3, 129.7, 130.5, 133.2, 167.2, 169.8. MS (FAB) m/z 387 (MH^+). Anal. Calcd for $C_{16}H_{22}N_2O_7S$: C, 49.73; H, 5.74; N, 7.25. Found: C, 49.49; H, 5.53; N, 7.59. Compound **7i**: Pale yellow powder, mp 120–122 °C. IR (KBr) ν_{max} 3147, 3011, 1781, 1598, 1577, 1449, 1099 cm^{-1}. ^{1}H NMR (400 MHz; DMSO-d_6+D_2O): 2.29 (s, 3H, Me), 4.07 (dd, 1H, $J_{1',2'} = 6.5$ Hz, $J_{1',NCH} = 5.4$ Hz, 1′-H), 4.19 (dd, 1H, $J_{5'Ha,Hb} = 10.1$ Hz, $J_{5'Hb,4'} = 5.7$ Hz, 5′-H_b), 4.39 (dd, 1H, $J_{1',2'} = 6.5$ Hz, $J_{2',3'} = 4.5$ Hz, 2′-H), 4.59 (dd, 1H, $J_{2',3'} = 4.5$ Hz, $J_{3',4'} = 4.3$ Hz, 3′-H), 4.76 (ddd, 1H, $J_{4',5'Ha} = 5.7$ Hz, $J_{4',5'Hb} = 5.7$ Hz, $J_{3',4'} = 4.3$ Hz, 4′-H), 4.88 (dd, 1H, $J_{5'Ha,Hb} = 10.1$ Hz, $J_{4',5'Ha} = 5.7$ Hz, 5′-H_a), 5.03 (dd, 1H,$J_{1',NCH} = 5.4$ Hz, $J_{SCH,NCH} = 4.5$ Hz, NCH), 6.69 (d, 1H, $J_{SCH,NCH} = 4.5$ Hz, SCH), 7.11–8.01 (m, 10H_{arom}). ^{13}C NMR (DMSO-d_6): δ 20.1, 35.5, 64.5, 65.3, 69.8, 71.4, 72.5, 73.3, 74.3, 126.2, 127.1, 127.8, 128.6, 129.5, 130.2, 130.9, 132.0, 132.9, 133.6, 167.5, 191.8. MS (FAB) m/z 509 (MH^+). Anal. Calcd for $C_{23}H_{28}N_2O_7S_2$: C, 54.31; H, 5.55; N, 5.51. Found: C, 53.97; H, 5.77; N, 5.34.

29. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
30. Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753–756.
31. Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675–4678.
32. Hirayama, M.; Gamoh, K.; Ikekawa, N. *Chem. Lett.* **1982**, 491–494.
33. Tanikaga, R.; Hamamura, K.; Kaji, A. *Chem. Lett.* **1988**, 977–980.