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Diastereospecific synthesis of novel tetracyclic β-lactams via 6-*exo*-*trig* radical cyclization

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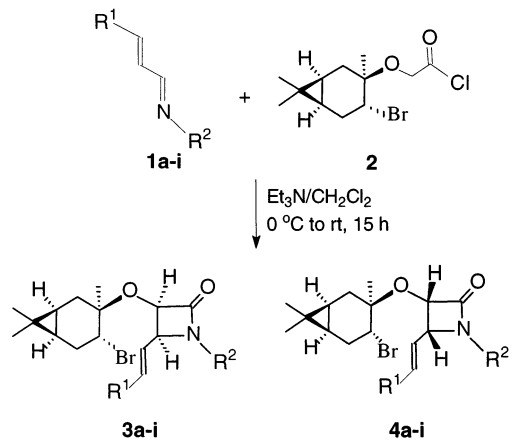
Abstract—An efficient and diastereospecific synthesis of a tetracyclic, 3.6.6.4 ring system fused to a β-lactam has been achieved in high yield via 6-*exo*-*trig* radical cyclization. © 2002 Elsevier Science Ltd. All rights reserved.

The stereoselective synthesis of complex heterocycles and carbocycles by radical cyclization has now been established as an efficient methodology in organic chemistry.[1] However, there are very few reports on the synthesis of multicyclic β-lactams via radical cyclization[2] and radical cyclizations involving C(3) and C(4) appendages of the 2-azetidinone have been far less investigated.[3] In our ongoing project on the asymmetric synthesis of β-lactams using halocarane,[4] we had access to a bicyclic ring system with a radical progenitor and a radical acceptor appended at C(3) and C(4), respectively of the β-lactam ring skeleton. Interestingly, in these substrates, the radical progenitor and acceptor are ideally placed for a 6-*exo* heptenyl radical cyclization. We, herein report a highly efficient and diastereospecific synthesis of novel tetracyclic β-lactams via 6-*exo* heptenyl radical cyclization.

The radical precursors **3** and **4** were easily accessible by diastereoselective synthesis (Scheme 1) via cycloaddition reaction of imines **1** with the chiral acid chloride **2**, derived from enantiomerically pure (+)-3-carene by following our earlier reported procedure.[4] In some cases the diastereomers (**3a**, **3c** and **4a**, **4b**, **4d**) were separated either by flash column chromatography or crystallization and well characterized by spectroscopic methods.

When the major diastereomer **3a** (0.1 M in benzene) was subjected to Bu_3SnH/AIBN-mediated radical cyclization, an excellent yield of tetracyclic β-lactam **5a**,[5,6] as a single diastereomer (HPLC, NMR) was achieved within 30 min (Scheme 2). Disappearance of the olefinic protons of the styryl group and the appearance of a doublet at δ 2.95 for two benzylic protons in the ^{1}H NMR spectrum of **5a**, indicated that the product is formed exclusively by 6-*exo*-*trig* cyclization.[7] Similarly, the minor diastereomer **4a** also underwent 6-*exo*-heptenyl radical cyclization with complete stereocontrol to give the tetracyclic product **6a**[8] as a crystalline solid, in excellent yield. The facility of this cyclization was



1,3,4	R^1	R^2
a	Ph	PMP
b	Ph	Ph
c	CH_3	Ph
d	Ph	*t*-Butyl
e	Ph	*n*-propyl
f	Ph	Cyclohexyl
g	Ph	(+)-(*R*)-α-methylbenzyl
h	Ph	-CH=CH_2
i	Ph	-CH=$CHCH_3$

Scheme 1.

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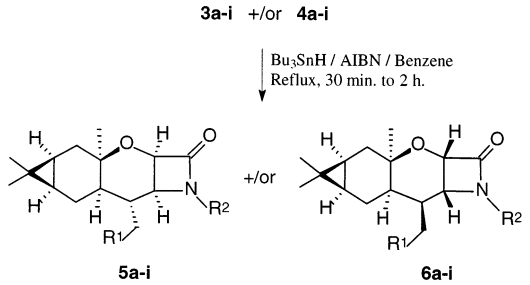

Scheme 2.

particularly noteworthy in the light of slow cyclization rates previously reported for 6-*exo* heptenyl radical cyclizations.[9]

The relative stereochemistry of the cyclized products **5a** and **6a** was deduced from the 2D COSY and ROESY NMR (500 MHz) spectral analysis (Fig. 1).

The assignment of the relative stereochemistry of these compounds was further ascertained from the single crystal X-ray structure determination of **6a** (Fig. 2).[10] The ORTEP diagram of **6a** showed that the molecule has a well spaced linear structure. It also illustrated that

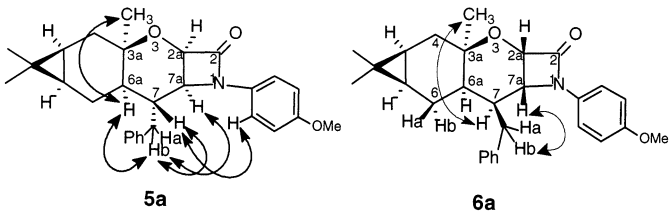

Figure 1. Important ROESY spatial correlations in **5a** and **6a**.

the newly formed pyran ring attains an inverted boat conformation with equatorial disposition of the benzylic group and β-lactam ring.

In order to ascertain the scope of this ring construction, we examined the cyclization of analogous substrates. Other diastereo-pure substrates **3c**, **4b** and **4d** also underwent smooth cyclization to give corresponding tetracyclic β-lactams **5c**, **6b** and **6d** stereospecifically, in very high yield (Table 1).[11] Similarly, radical cyclization of the diastereomeric mixtures **3b**, **3e–i** and **4b**, **4e–i** afforded corresponding mixtures of two tetracyclic compounds **5b**, **5e–i** and **6b**, **6e–i** (^{1}H NMR) in the same diastereomeric ratio as that of the starting material, which indicates that each diastereomer cyclizes stereospecifically to the corresponding tetracyclic product.

The exceptionally high stereoselectivity in this 6-*exo-trig* cyclization leading to cyclized products **5** and **6** can be rationalized by invoking a six-membered transition state model.[12] The conformational constraint within the rigid bicyclic system and β-lactam framework with a flexible oxygen tether does not allow the system to go through the generally favored 6-*exo*-chair transition state and the energetically favored six-membered boat-like[13] transition states **A** and **C** seem to be involved in the cyclization of **3** and **4**, leading stereospecifically to cyclic products **5** and **6**, respectively (Fig. 3). The transition states **B** and **D** are not favored for cyclization as they involve relatively high steric interactions between the double bond and the β-lactam ring.

In summary, we have reported an exceptionally efficient, diastereospecific 6-*exo-trig* radical cyclization, which involves a rare boat-like transition state. The cyclization provides ready access to a highly strained homochiral tetracyclic 3.6.6.4 ring system containing a fused β-lactam ring.

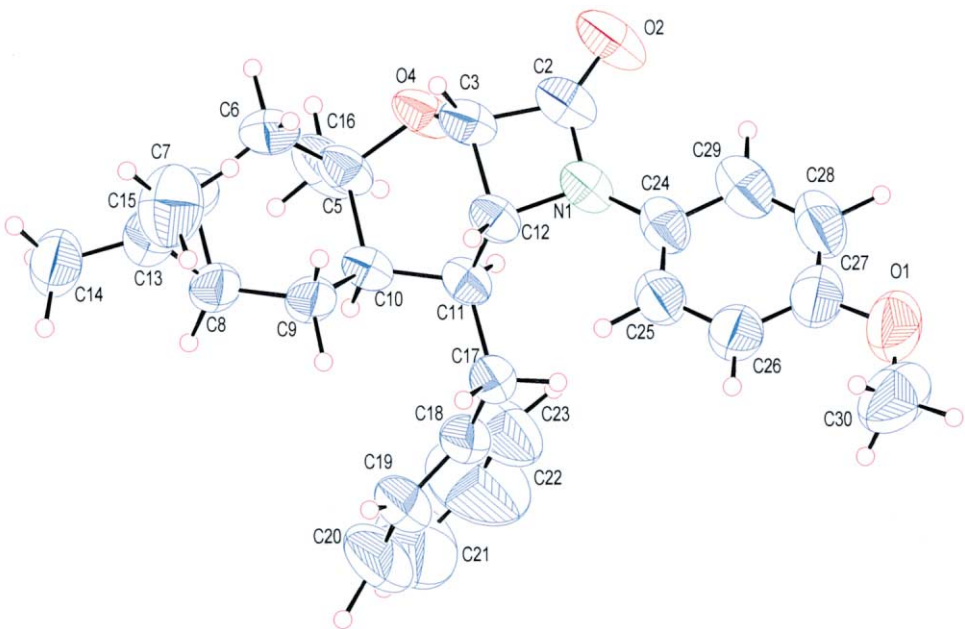

Figure 2. ORTEP diagram of **6a**.

Table 1. Radical cyclization of β-lactams **3a–i** and **4a–i**

Reactant no.	R^1	R^2	Product no.	Yield[a] (%)	Time (h)	Mp (°C)	$[\alpha]_D$ (CH_2Cl_2)
3a	Ph	PMP	**5a**	96	0.5	58–59	−8.75 (*c* 6.16)
3b+**4b**[b]	Ph	Ph	**5b**+**6b**[c]	83	2	–	–
3c	CH_3	Ph	**5c**	91	2	116–118	+79.8 (*c* 0.99)
4a	Ph	PMP	**6a**	96	0.5	196–197	+22.6 (*c* 1.28)
4b	Ph	Ph	**6b**	80	1	186–188	+20.5 (*c* 0.76)
4d	Ph	*t*-Butyl	**6d**	90	1	132–134	+21.8 (*c* 0.78)[d]
3e+**4e**[b]	Ph	*n*-Propyl	**5e**+**6e**[c]	65	1	–	–
3f+**4f**[b]	Ph	Cyclohexyl	**5f**+**6f**[c]	70	2	–	–
3g+**4g**[b]	Ph	(+)-*R*-α-Methylbenzyl	**5g**+**6g**[c]	76	2	207–208[e]	+24.1 (*c* 0.55)[e]
3h+**4h**[b]	Ph	-CH=CH_2	**5h**+**6h**[c]	60	2	–	−7.8 (*c* 2.5)[f]
3i+**4i**[b]	Ph	-CH=$CHCH_3$	**5i**+**6i**[c]	65	2	–	–

[a] Isolated yields.
[b] Diastereomeric mixture (~60:40) was used for radical cyclization.
[c] A mixture of two cyclized products was isolated in same diastereomeric ratio.
[d] Optical rotation recorded as $CHCl_3$ solution.
[e] Mp and specific rotation of pure **6g** obtained from **5g**+**6g** by crystallization.
[f] Specific rotation of pure **5h** obtained by column chromatography.

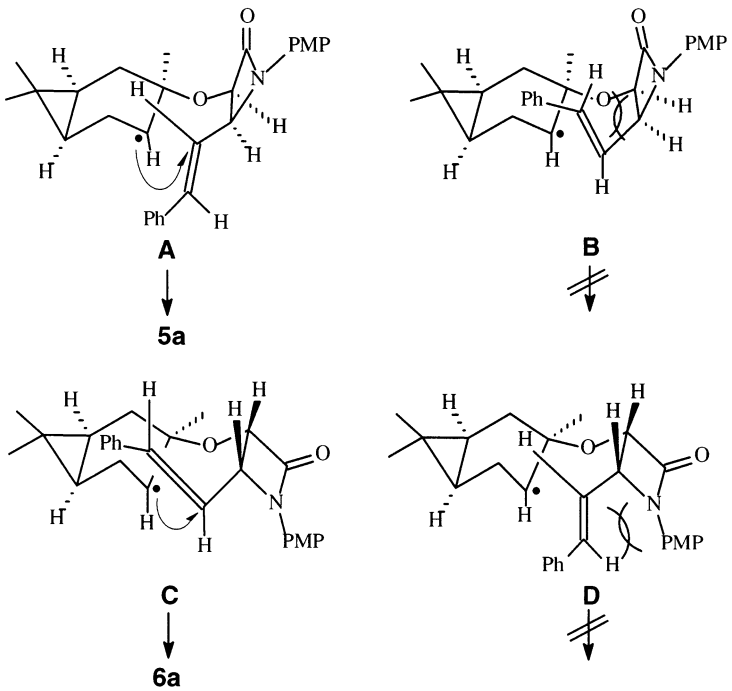

Figure 3. Possible transition states for the formation of **5a** and **6a**.

Acknowledgements

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5. *Typical procedure for radical cyclization*: Bu_3SnH (1.5 equiv.) was added over a period of 5 min to a refluxing solution of β-lactam **3** and/or **4** (1 equiv.) and AIBN (catalytic) in benzene (15 mL). The reaction mixture was further heated under reflux for 1–2 h. After completion of the reaction (TLC), the solvent was removed on rotary evaporator under reduced pressure to give cyclized product **5** or **6**. The crude reaction mixture was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, 230–400 mesh, petroleum ether/ethyl acetate, 92:10).
6. Data for **5a**: mp 58–59°C; $[\alpha]_D^{25}$ −8.75 (*c* 6.16, CH_2Cl_2); IR 1740 cm^{-1}; ^{1}H NMR δ 0.35–0.50 (m, 2H), 0.95 (s, 3H), 1.0 (s, 3H), 1.0–1.05 (m, 1H), 1.35–1.42 (m, 1H), 1.43 (s, 3H), 1.55–1.75 (m, 3H), 2.43–2.55 (m, 1H), 2.95 (d, J=7.8 Hz, 2H), 3.78 (s, 3H), 3.95 (dd, J=1.70, 5.60 Hz, 1H), 4.94 (d, J=5.60 Hz, 1H), 6.82 (dd, J=2, 9 Hz, 2H), 7.15 (dd, J=2, 9 Hz, 2H), 7.26–7.28 (m, 3H), 7.36 (t, J=7.5 Hz, 2H); ^{13}C NMR δ 14.77, 18.51, 19.84, 21.85, 26.59, 27.98, 31.37, 32.61, 38.95, 40.13, 40.35, 52.46, 53.13, 55.13, 75.43, 77.04, 114.35, 118.47, 126.25, 128.41, 128.65, 130.38, 139.58, 156.22, 166.43; MS *m*/*z* 432 (M+ 1, 2), 431 (M$^+$, 5), 93 (100). Anal. calcd for $C_{28}H_{33}NO_3$: C, 77.91; H, 7.71; N, 3.25. Found C, 77.98; H, 7.60; N, 3.43%.
7. The cyclization reaction was stereospecific and no trace of the uncyclized reduction product was observed in the ^{1}H NMR spectrum of the crude reaction mixture.
8. Data for **6a**: mp 197°C; $[\alpha]_D^{25}$ +22.6 (*c* 1.25, CH_2Cl_2); IR 1740 cm^{-1}; ^{1}H NMR δ 0.35–0.47 (m, 2H), 0.65–0.75 (m, 1H), 1.0 (s, 3H), 1.06 (s, 3H), 1.18 (s, 3H), 1.20–1.25 (m, 1H), 1.30–1.35 (m, 1H), 1.59–1.63 (m, 1H), 1.89–1.94 (m, 1H), 2.40–2.45 (m, 1H), 2.70 (dd, J=12.5, 13.5 Hz, 1H), 3.13 (dd, J=4.5, 13.5 Hz, 1H), 3.78 (s, 3H), 3.94 (dd, J=4.6, 9.4 Hz, 1H), 4.75 (d, J=4.6 Hz, 1H), 6.87 (dd, J=2, 9 Hz, 2H), 7.11 (d, J=7.5 Hz, 2H), 7.18–7.28 (m, 3H), 7.38 (d, J=9 Hz, 2H); ^{13}C NMR δ 14.87, 17.61, 18.49, 18.67, 21.49, 27.14, 28.12, 29.49, 31.06, 36.73, 38.69, 39.32, 55.53, 55.89, 74.03, 77.66, 119.84, 126.21, 128.24, 128.41, 130.87, 138.57, 156.55, 163.99; MS *m*/*z* 432 (M$^+$+1, 11), 431 (M$^+$, 38), 165 (100). Anal. calcd for $C_{28}H_{33}NO_3$: C, 77.91; H, 7.71; N, 3.25. Found C, 77.88; H, 7.84; N, 3.47%.
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10. X-Ray crystal data for **6a**: $C_{28}H_{33}rNO_3$, M_r=431.55, a=6.830 (2), b=19.400 (4), c=18.439 (4) Å, α=90°, β=90°, γ=90°, V=2443.2 (10) Å 3, Z=4, ρ_{calcd}=1.173 Mg m^{-3}, R_w=0.1968, T=293 (2) K, GOF, 0.966. Data were collected on Enariuf Nonius CAD-4 single crystal X-ray diffractometer using Cu Kα radiation (λ=0.70930 Å) and ω–2θ scan mode to a θ range of 1.52 to 24.88°. The structure was solved by direct positional and anisotropic thermal parameters for non-hydrogen atom converged to R_w=0.1764 R_1=0.0691 for 4240 unique observed reflections. Hydrogen atoms were geometrically fixed and confirmed by a difference fourier was held fixed during the refinement. The refinements were carried out using SHELEX-97.
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