Pergamon

Tetrahedron Letters 43 (2002) 2721–2723

TETRAHEDRON LETTERS

An efficient synthesis of γ-substituted α,β-unsaturated δ-lactams. Formal synthesis of (±)-protoemetinol

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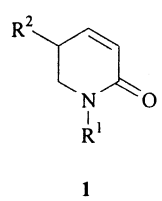
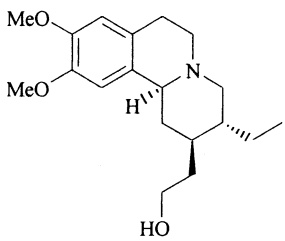
Received 11 January 2002; revised 12 February 2002; accepted 22 February 2002

Abstract—γ-Substituted α,β-unsaturated δ-lactams **1** was synthesized from α-sulfinyl acetamides **3** in three steps. Formal synthesis of (±)-protoemetinol was also reported.

A great number of piperidine-containing compounds are biologically and medicinally interesting.[1] As a consequence, the development of general methods for the synthesis of piperidine derivatives has been the subject of considerable synthetic efforts.[2] The addition of stabilized anions[3] and organocuprates[4] to γ-substituted α,β-unsaturated δ-lactams **1** has been used as a method for the stereoselective synthesis of *cis*- and *trans*-3,4-disubstituted piperidine.[2] In this report, we describe an efficient preparation of γ-substituted α,β-unsaturated δ-lactams **1**[5] and a formal synthesis of (±)-protoemetinol (**2**).



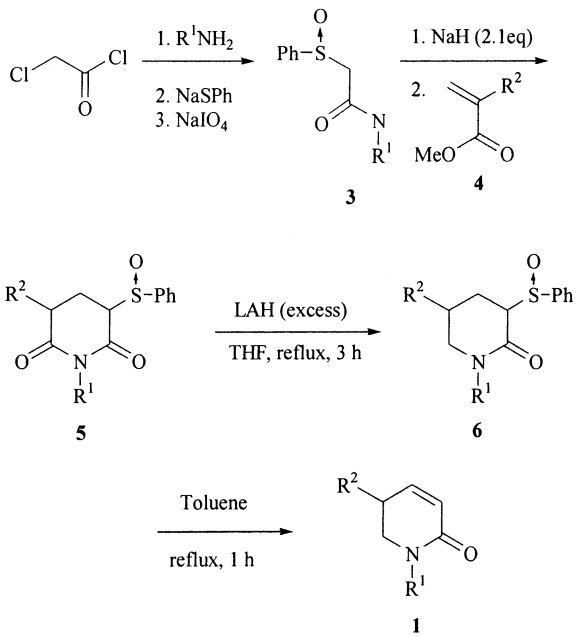
1



(±)-Protoemetinol (**2**)

For the synthesis of **1**, the required α-sulfinyl acetamides **3** were prepared by sequential treatment of chloroacetyl chloride with appropriate amines, sodium thiophenoxide, followed by oxidation of the resulting sulfides with sodium periodate. After reaction of **3** with sodium hydride (2.1 equiv.) for 1 min, the resulting dianion reacted with various γ-substituted α,β-unsaturated esters at 25°C to afford the corresponding [3+3] cycloaddition products **5**.[6] Regioselective reduction of **5** with excess lithium aluminum hydride (3 equiv.) in refluxing THF solution for 3 h gave diastereomer lactam **6**. Finally, refluxing of **6** in toluene solution yielded the elimination products **1** (Scheme 1).

For unknown reasons both glutarimides **5** and lactams **6** proved to be unstable, easily affording the corresponding oxidized derivatives **7** and **8** during chromatographing.[8] As a consequence, they were prepared immediately before the next reaction and used without further purification. As summarized in Table 1, using this protocol, various γ-substituted α,β-unsaturated δ-lactams **1** were produced in reasonable yields.



Scheme 1.

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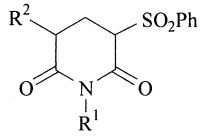
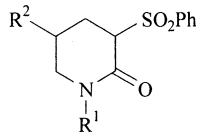
PII: S0040-4039(02)00401-X

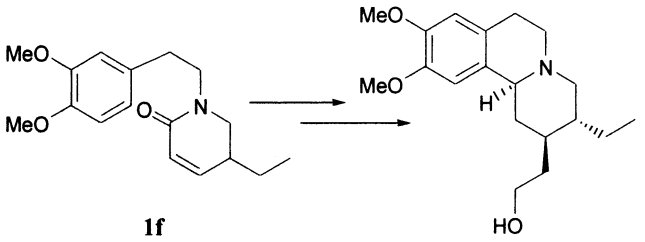


7d R^1=Me R^2=Bn



8d R^1=Me R^2=Bn

Since lactam **1f** has already been converted to (**2**),[9] the above investigations provided a new way for the racemic synthesis of alangium alkaloids (±)-protoemetinol (Scheme 2).



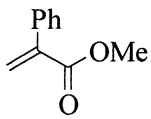
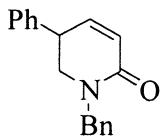
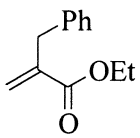
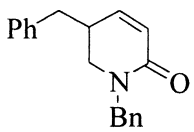
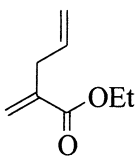
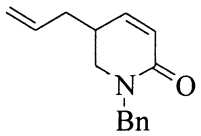
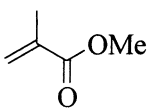
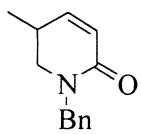
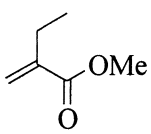
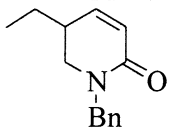
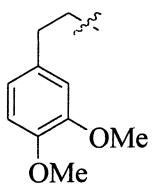
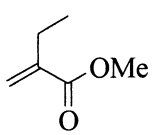
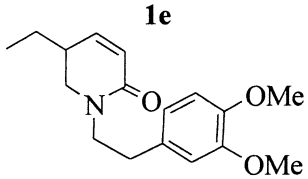
1f

(±)-Protoemetinol (**2**)

Scheme 2.

In conclusion, we have developed a new direct route to γ-substituted α,β-unsaturated lactams **1** in three steps starting from **3**. Further application of this methodology in the synthesis of polysubstituted piperidines and pyridones are currently underway in our laboratory.

Table 1. Formation of γ-substituted α,β-unsaturated δ-lactams

Entry	R_1	Michacl acceptor	Product	Yield
a	Bn		 **1a**	40%
b	Bn		 **1b**	42%
c	Bn		 **1c**	41%
d	Bn		 **1d**	46%
e	Bn		 **1e**	42%
f			 **1f**	44%

[a] All the yields were based on α-sulfinyl acetamides 3.

[b] For selected NMR spectral data for **1b, 1c, 1d, 1f** see Ref. 7.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for financial support.

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7. Selected spectral data of **1b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.19 (m, 8H), 6.87 (d, $J=6.5$ Hz, 1H), 6.48 (dd, $J=3.5$, 10 Hz, 1H), 6.00 (d, $J=10$ Hz, 1H), 4.80 (d, $J=14.5$ Hz, 1H), 4.38 (d, $J=14.5$ Hz, 1H), 3.33 (dd, $J=5.5$, 12.5 Hz, 1H), 3.09 (dd, $J=5.5$, 12.5 Hz, 1H), 2.68–2.6 (m, 2H), 2.50 (dd, $J=7.5$, 12 Hz, 1H); **1c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 6.48 (dd, $J=4$, 10 Hz, 1H), 5.99 (dd, $J=1.5$, 10 Hz, 1H), 5.65–5.56 (m, 1H), 5.00 (d, $J=9.5$ Hz, 1H), 4.85 (d, $J=17.5$ Hz, 1H), 4.65 (d, $J=14$ Hz, 1H), 4.54 (d, $J=14$ Hz, 1H), 3.34 (dd, $J=6$, 12.5 Hz, 1H), 3.13 (dd, $J=8$, 12.5 Hz, 1H), 2.48–2.46 (m, 1H), 2.15–2.00 (m, 2H); **1d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.26 (m, 5H), 6.41 (dd, $J=3.5$, 10Hz, 1H), 5.94 (dd, $J=2.10$ Hz, 1H) 4.61 (s, 2H), 3.31 (dd, $J=6$, 12 Hz, 1H), 3.03 (dd, $J=9.5$, 12 Hz, 1H), 2.59–2.57 (m, 1H), 1.00 (d, $J=7.5$ Hz, 3H); **1f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82–6.77 (m, 3H), 6.47 (dd, $J=3.5$ Hz, 10 Hz, 1H), 6.01 (dd, $J=1.5$, 10 Hz, 1H), 3.90–3.82 (m, 6H), 3.71–3.65 (m, 1H), 3.59–3.53 (m, 1H), 3.27 (dd, $J=6.5$, 12.5 Hz, 1H), 3.11 (dd, $J=9$, 12.5 Hz, 1H), 2.84 (t, $J=7.5$ Hz, 2H), 2.29–2.28 (m, 1H), 1.48–1.43 (m, 1H), 1.38–1.32 (m, 1H), 0.90 (t, $J=8$ Hz, 3H).
8. Selected spectral data of **7d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66–7.62 (m, 3H), 7.48 (t, $J=7$ Hz, 2H), 7.33–7.25 (m, 5H), 5.00 (d, $J=14$ Hz, 1H), 4.88 (d, $J=14$ Hz, 1H), 4.12 (dd, $J=2$, 6.5 Hz, 1H), 3.36–3.31 (m, 1H), 2.89–2.85 (m, 1H), 2.07–2.00 (m, 1H), 1.33 (d, $J=7$ Hz, 3H); **8d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, $J=7.5$ Hz, 2H), 7.65 (t, $J=7.5$ Hz, 1H), 7.58–7.54 (m, 2H), 7.35–7.25 (m, 3H), 7.16 (d, $J=7.5$ Hz, 2H), 4.60 (d, $J=14.5$ Hz, 1H), 4.47 (d, $J=14.5$ Hz, 1H), 4.19 (dd, $J=7.5$, 11 Hz, 1H), 3.09–3.05 (m, 1H), 2.99 (t, $J=12$ Hz, 1H), 2.49–2.44 (m, 1H), 2.14–1.95 (m, 2H), 1.03 (d, $J=6.5$ Hz, 3H).
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