Pergamon

Tetrahedron Letters 42 (2001) 4467–4469

TETRAHEDRON LETTERS

A straightforward enantiospecific synthesis of *N*-(*Z*)-galantinic butyl ester

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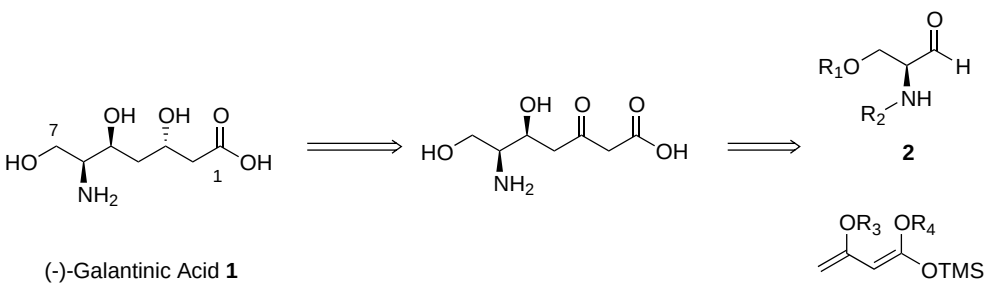
Received 9 April 2001; revised 2 May 2001; accepted 6 May 2001

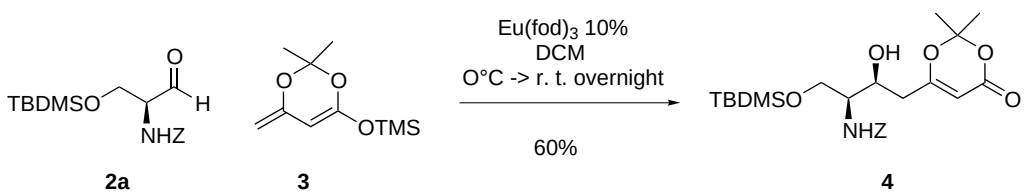
Abstract—A short and efficient access to the naturally occurring amino acid galantinic acid is reported using two highly diastereoselective reactions, namely a vinylogous Mukaiyama reaction and a 1,3-hydroxy directed Evans reduction. © 2001 Elsevier Science Ltd. All rights reserved.

The natural amino acid galantinic acid **1** is a key component of Galantin I, a potent peptide antibiotic isolated from *Bacillus pulvifaciens*.[1] Due to its original structure and biological activity, the synthesis of galantinic acid has prompted several reports.[2] In connection with an ongoing project directed towards the development and applications of vinylogous Mukaiyama-aldol reactions,[3] we planned (Scheme 1) to construct the galantinic acid carbon skeleton using a Lewis acid catalyzed acetoacetate aldol-type reaction[4–6] on a protected serinal **2**. The C5(OH)–C6(NH) *syn* relationship was expected to be fixed during this step through chelation control.[7]

The reaction of known[8] serinal aldehyde **2a** (R_1 = TBDMS, R_2 = Z) with dienolate **3**,[9] in the presence of 10% of $Eu(fod)_3$ led to the formation of the vinylogous aldol product **4** with a good (9:1) diastereoselectivity.[10] After purification by flash chromatography, compound **4**[11] was isolated in 60% yield, and >98:2 diastereoselectivity (Scheme 2).



Scheme 1.



Scheme 2.

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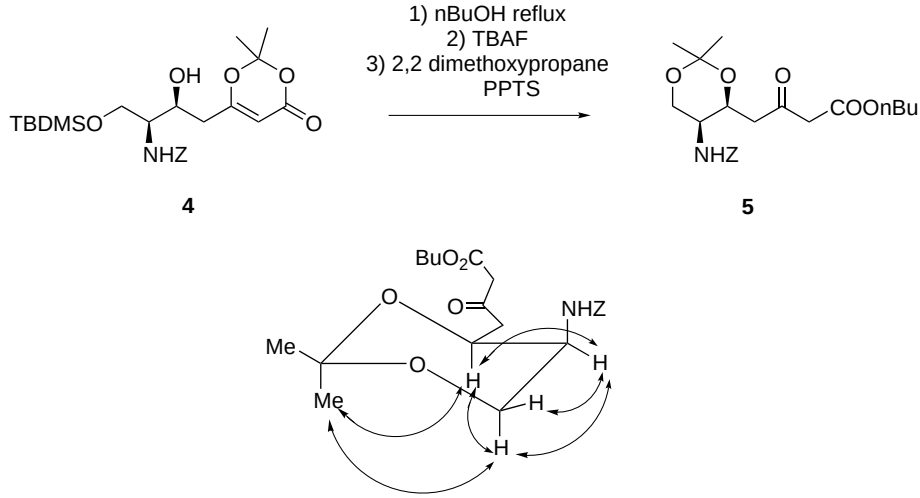
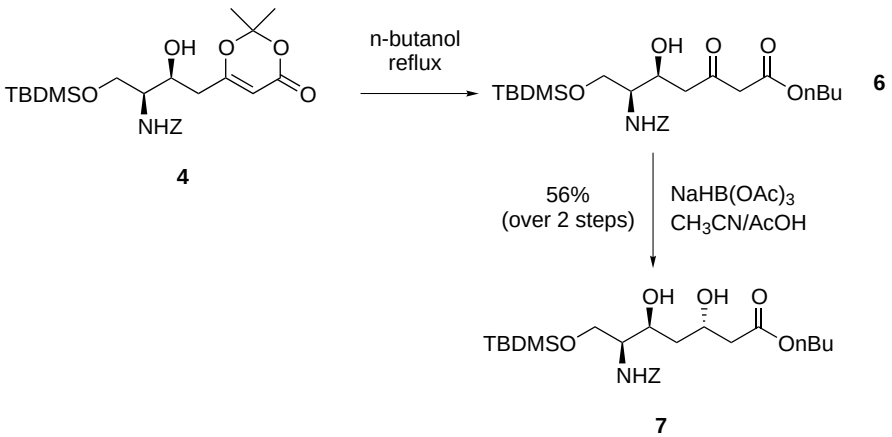
PII: S0040-4039(01)00753-5



Scheme 3.



Scheme 4.

The expected C5(OH)–C6(NH) *syn* relationship was confirmed by conducting a 400 MHz NOESY NMR experiment on compound **5** (Scheme 3), synthesized in three steps (30% yield) from **4**.

The C5(OH)–C6(NH) *syn* relationship thus established, the dioxinone ring was opened-up[6c] by refluxing **4** in butanol at 120°C, to give the keto-alcohol **6**. Compound **6** was found to be quite unstable towards purification by flash chromatography, and was directly used, in the next reaction, without purification. Reduction of the 3,5-keto-alcohol **6**, under Evans conditions,[2c,12] led after purification to the galantinic butyl ester **7**[13] in 56% yield (over two steps) and 98:2[14] diastereoselectivity (Scheme 4).

In conclusion, we have developed, starting from protected serinal **2a**, an efficient and short access (three steps) to galantinic acid, based on two highly diastereoselective reactions, namely a vinylogous Mukaiyama-aldol reaction and an Evans hydroxy directed ketone reduction.

Acknowledgements

The authors are grateful to M.-T. Martin for the NOESY experiment and to Dr. J. Poncet for the HPLC determination of diastereoselectivity on compounds **4** and **7**.

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10. The diastereoselectivity was determined by HPLC (Ultrasphere 250×4.6 mm; *i*PrOH/hexane 3/97; 1 ml/min) on the crude material.
11. Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H), 5.41 (bd, $J=9$ Hz, 1H), 5.32 (s, 1H), 5.11 (s, 2H), 4.27 (m, 1H), 3.85 (~d, $J=3$ Hz, 2H), 3.64 (~d, 1H), 3.34 (s, 1H), 2.4 (m, 2H), 1.67 (s, 6H), 0.88 (s, 9H), 0.055 and 0.048 (2s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 168.35, 160.35, 156.32, 136.20, 128.52, 128.20, 128.05, 106.55, 95.26, 69.69, 66.96, 65.71, 54.11, 38.44, 25.70, 25.23, 24.66, 18.05, −5.50; IR ($CHCl_3$): 3684, 3012, 1718, 1521, 1237, 793 cm^{-1}; MS (ESI, %): 518 ($M+K^+$) (68), 502 ($M+Na^+$) (100), 485.5 (12), 443 (25), 242 (33); $[\alpha]_D^{25}=1.64$ (*c* 0.7, $CHCl_3$). Anal. calcd for $C_{24}H_{37}NO_7Si$: C, 60.10; H, 7.78; N, 2.92. Found: C, 59.84; H, 7.76; N, 3.01.
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13. Compound **7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35 (m, 5H), 5.44 (bd, $J=9.0$ Hz, 1H), 5.1 (bs, 2H), 4.3 (m, 2H), 4.1 (t, $J=6.6$ Hz, 2H), 3.86 (bs, 2H), 3.6 (~d, $J=8.8$ Hz, 1H), 2.48 (bd, $J=6.0$ Hz, 2H), 1.75–1.50 (m, 4H), 1.40 (m, 2H), 0.95 (t, $J=7.3$ Hz, 3H), 0.88 (s, 9H), 0.055 and 0.042 (2s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 173.15, 156.74, 136.71, 128.77, 128.38, 128.30, 69.83, 67.07, 66.36, 65.39, 64.89, 55.14, 41.62, 40.16, 30.81, 26.00, 19.34, 18.36, 13.91, −5.40; IR ($CHCl_3$): 3441, 1723 cm^{-1}; MS (ESI, %): 536 (30), 520 ($M+Na^+$) (100), 498 ($M+H^+$) (30), 236 (30); $[\alpha]_D^{25}=+15.45$ (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{25}H_{43}NO_7Si$: C, 60.33; H, 8.71; N, 2.81. Found: C, 60.56; H, 8.91; N, 2.66.
14. On the crude material, the diastereoselectivity was found (HPLC: Ultrasphere 250×4.6 mm; *i*PrOH/cyclohexane 1.5/98.5; 1 ml/min) to be 88:12, by comparison with a 43:57 sample obtained by a non-diastereoselective reduction using $NaBH_4$ in THF.