Synthesis of Functionalized Cyclopentane for Pactamycin, a Potent Antitumor Antibiotic

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Abstract: A tricyclic compound including a cyclopentane structure for pactamycin, an antitumor antibiotic, was constructed by Overman rearrangement and Pauson–Khand cyclization as key steps starting from diacetone-D-glucose.

Key words: pactamycin, natural products, antibiotics, Overman rearrangement, Pauson–Khand reaction

Pactamycin was isolated as a potent antitumor antibiotic from a fermentation broth of *Streptomyces pactum* var *pactum*.[1] From the same fermentation broth was isolated pactamycate, a derivative of pactamycin.[2] The structure of these compounds was elucidated in 1969 from NMR analyses and chemical degradation.[3] However, X-ray crystallographic analysis of a derivative of pactamycate revised the structure to be **1** and revealed the absolute stereochemistry (Figure 1).[4] Pactamycin shows potent in vitro and in vivo antitumor activity as well as antimicrobial activity.[1a,5] The action mechanism is inhibition of protein synthesis[6] through binding to the ribosomal small subunit.[7] The structural feature of pactamycin is a densely functionalized cyclopentane ring including three contiguous quaternary carbons with oxygen or nitrogen functionalities such as substituted benzoic acid, *m*-acyl aniline and dimethyl urea. Surprisingly, despite their unprecedented complex structures as well as potent biological activities, little synthetic study on pactamycin has been reported since its structure determination. We disclose herein our efforts toward the synthesis of pactamycin.

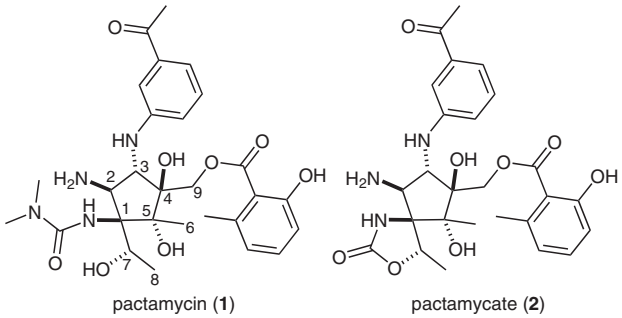
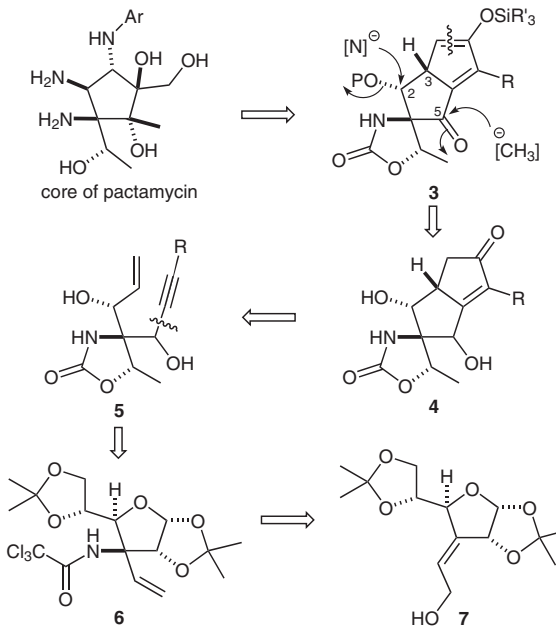


Figure 1 The structures of pactamycin and pactamycate.

Our synthetic plan is illustrated in Scheme 1. The core structure of pactamycin was envisaged to be synthesized from a tricyclic compound **3**; the amino group at the C-2 position would be installed by nucleophilic substitution in S_N2 manner, while the nitrogen function at the C-3 position would be introduced by Curtius rearrangement of a carboxylic acid, which could be obtained from oxidative cleavage of the silylenolether. Methyl group (C-6) would be introduced by addition of a methyl nucleophile to the ketone at the C-5 position. Since the enolether **3** would be obtainable from **4**, the compound **4** was regarded as an important intermediate. The cyclopentenone of **4** would arise from intramolecular Pauson–Khand reaction[8] of enyne **5**. The acetylenic moiety could be introduced by addition of acetylide to an aldehyde, while the vinyl group would be prepared from diol. Thus, enyne **5** was retrosynthesized into **6**. The nitrogen function connected to a quaternary carbon center would be introduced by Overman rearrangement[9] from the known *exo*-allylic alcohol **7**.[10]



Scheme 1 Synthetic plan for pactamycin.

The *exo*-allylic alcohol **7**, readily prepared from a commercially available diacetone-D-glucose **8**,[11] was treated with trichloroacetonitrile and DBU to give a labile allylic

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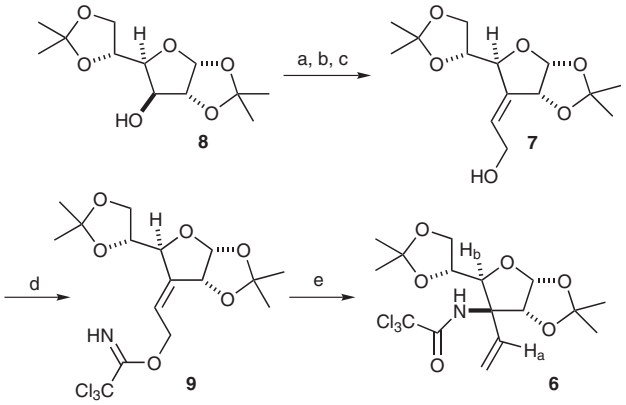
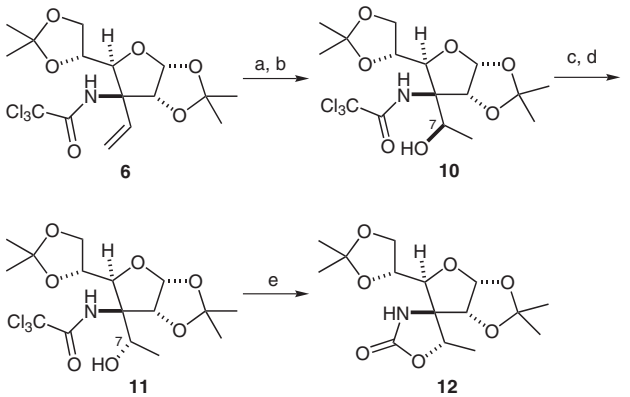
trichloroacetimidate **9** (Scheme 2). The Overman rearrangement of **9** was carried out in refluxing xylene in the presence of K_2CO_3[12] to afford the desired trichloroacetamide **6** as a single product in 90% yield from **7**.[13] The configuration of the newly generated asymmetric center of **6** was confirmed by the observation of NOESY correlation between H_a and H_b as shown in Scheme 2. Since it was reported the Overman rearrangement of **9** in the absence of K_2CO_3 failed to give **6**,[14] this experiment demonstrates K_2CO_3 is a crucial additive for the successful Overman rearrangement.



Scheme 2 *Reagents and conditions*: a) TPAP, NMO, MS 4 Å, MeCN; b) $Ph_3P{=}CHCO_2Et$, toluene, 100 °C (73% from **8**); c) DIBALH, CH_2Cl_2, –20 °C (99%); d) Cl_3CCN, DBU, CH_2Cl_2, –78 °C; e) K_2CO_3, *p*-xylene, reflux (90% from **7**).

A hydroxyl group at C-7 (pactamycin numbering) was introduced as shown in Scheme 3. Ozonolysis[15] of the vinyl group of **6** gave neopentyl aldehyde (90% yield), which was treated with methylmagnesium bromide to afford carbinol **10** as a single product (95% yield).[16] Since the configuration at C-7 was opposite to that of pactamycin judging from the NOESY spectra (vide infra), the configuration was inverted by oxidation of the alcohol with DMSO and Ac_2O followed by Luche reduction[17] to preferentially afford the desired isomer **11** in 70% yield along with **10** in 10% yield. The stereochemistry of carbinol **10**



Scheme 3 *Reagents and conditions*: a) O_3, CH_2Cl_2, –78 °C, then Et_3N, 0 °C (90%); b) MeMgBr, THF, 0 °C (95%); c) DMSO, Ac_2O, r.t. (96%); d) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_2Cl_2–MeOH, –10 °C (**11**: 70%, **10**: 10%); e) DBU, CH_2Cl_2, r.t. (99%).

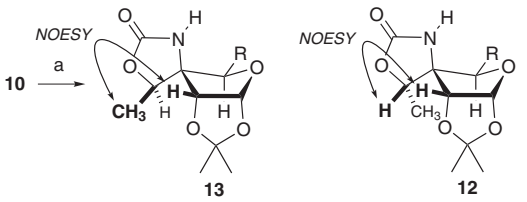
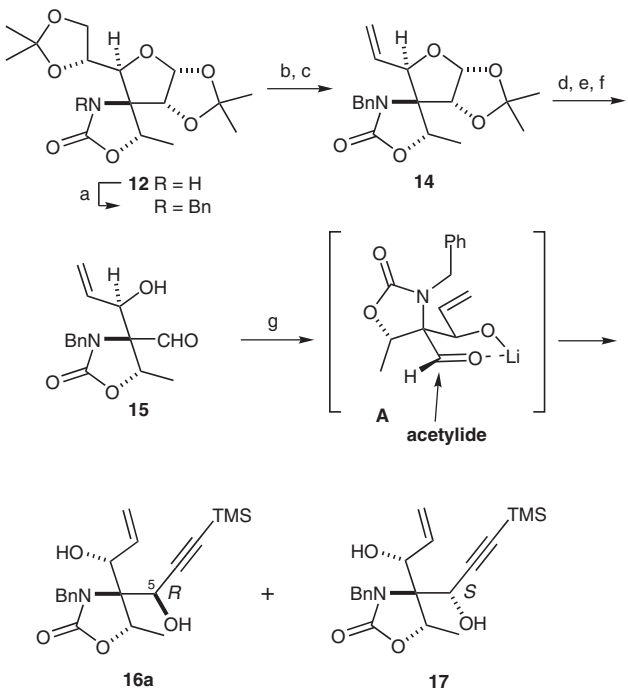


Figure 2 *Reagents and conditions*: a) DBU, CH_2Cl_2, r.t. (90%).

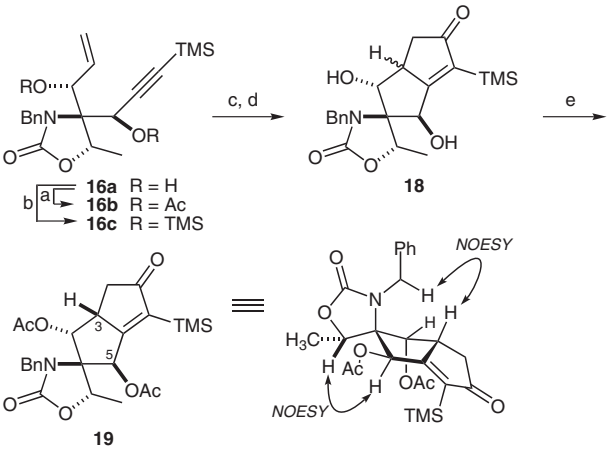
and **11** was confirmed by the NOESY spectra of the corresponding oxazolidinones **12** and **13** derived from **11** and **10**, respectively (Figure 2).[18]

We next elaborated two acetonides of **12** to precursors for the cyclization (Scheme 4). After the benzylation of oxazolidinone **12**, the terminal acetonide was converted to a vinyl group in 2 steps; acidic deprotection of the acetonide and reductive olefination according to the Tipson–Cohen procedure.[19] The other acetonide was removed with 80% aqueous TFA. The resulting hemiacetal was reduced with $NaBH_4$ to give a triol, in which the vicinal diol was cleaved with $NaIO_4$ to afford unstable β-hydroxyaldehyde **15**. To this aldehyde **14** was added (2-trimethylsilyl)ethynyllithium to afford a mixture of diols **16a**[20] (55% yield in 3 steps) and **17** (6% yield in 3 steps). The configuration of the C-5 position could not been determined at this stage. However, we expected that the major product **16a** had 5*R*-configuration from the following consideration; a six-membered chelation structure as **A** might be attacked by the acetylide from the less hindered bottom side. The configuration was finally confirmed by NOESY spectra of **19** (vide infra).



Scheme 4 *Reagents and conditions*: a) NaH, DMF, BnBr, TBAI, r.t. (93%); b) 50% aq HOAc, r.t. (85%); c) MsCl, Et_3N, DMF, 0 °C then NaI, Zn, 120 °C (86%); d) 80% aq TFA, r.t. (90%); e) $NaBH_4$, MeOH, 0 °C; f) $NaIO_4$, THF, H_2O; g) *n*-BuLi, TMS-C≡CH, THF, 0 °C (**16a**: 55% in 3 steps, **17**: 6% in 3 steps).

With the precursors for the cyclization in hand, we examined intramolecular Pauson–Khand reaction (Scheme 5).[8,21] Enyne **16a** was treated with $Co_2(CO)_8$ to give the corresponding acetylene–cobalt complex, which was heated in MeCN at 70 °C to afford an inseparable mixture. Fortunately, when the crude material was treated with Ac_2O and pyridine at room temperature, the major product was transformed to diacetate **19**[22] as a single diastereomer in 55% yield from **16a** after silica gel column chromatography.[23] The configurations of the C-3 and C-5 positions of **19** were determined by the observation of the NOESY correlations as shown in Scheme 5. Interestingly, the diacetate **16b** and the bis-TMS ether **16c** and the diastereomeric isomer **17** did not undergo the Pauson–Khand reaction under the same conditions.



Scheme 5 *Reagents and conditions*: a) Ac_2O, pyridine (80%); b) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2 (90%); c) $Co_2(CO)_8$, CH_2Cl_2, r.t.; d) MeCN, 70 °C; e) Ac_2O, pyridine, r.t. (55% in 3 steps).

In summary, tricyclic compound **19** including all the carbon atoms for the core cyclopentane of pactamycin has been synthesized from diacetone-D-glucose. The product also possesses suitable structure for installation of the remaining functionalities. Further studies toward the total synthesis are in progress in this laboratory.

Acknowledgment

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(13) Spectral data of **6**: colorless crystalline solids, mp 116–118 °C; $[\alpha]_D^{26}$ +41.4 (*c* 1.05, $CHCl_3$). IR (NaCl, film): ν_{max} = 3312, 2990, 1720, 1507, 1375, 1248, 1216, 1164, 1081, 1007, 872, 844, 822 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35, 1.37, 1.49, 1.57 (each 3 H, s, acetonide), 3.96 (1 H, t, *J* = 8 Hz, H-6), 4.06 (1 H, dd, *J* = 8.0, 6.5 Hz, H6), 4.18 (1 H, d, *J* = 3.5 Hz, H-4), 4.56 (1 H, ddd, *J* = 8.0, 6.5, 3.5 Hz, H-5), 5.28 (1 H, d, *J* = 3.5 Hz, H-2), 5.43 (1 H, d, *J* = 11.0 Hz, CH=C*H*H), 5.44 (1 H, d, *J* = 17.5 Hz, CH=CH*H*), 5.92 (1 H, d, *J* = 3.5 Hz, H-1), 6.04 (1 H, dd, *J* = 17.5, 11.0 Hz, C*H*=CH_2), 8.54 (1 H, s, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 26.0, 26.5, 26.6, 66.0, 69.8, 75.4, 78.5, 83.7, 92.9, 103.9, 110.5, 112.4, 117.5, 131.0, 161.5 ppm. Anal. Calcd for $C_{16}H_{22}NO_6Cl_3$: C, 44.62; H, 5.15; N, 3.25. Found: C, 44.63; H, 5.12; N, 3.23.
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(20) Spectral data of **16a**: colorless oil; $[\alpha]_D^{26}$ +88.8 (*c* 0.16, $CHCl_3$). IR (NaCl, film): ν_{max} = 3413, 2960, 2175, 1724, 1414, 1250, 1075, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 (9 H, s, TMS), 1.52 (3 H, d, *J* = 7.0 Hz, CH_3), 2.49 (1 H, br, -O*H*), 2.85 (1 H, br, -O*H*), 4.58 (2 H, s, CH_2-Ph), 4.68 (1 H, br d, *J* = 5.0 Hz, CH_2=CH-C*H*-OH), 4.94 (1 H, s, C≡C-C*H*-OH), 4.97 (1 H, q, *J* = 7.0 Hz, C*H*CH_3), 5.37 (1 H, dt, *J* = 10.5, 1.5 Hz, CH_AH_B=CH), 5.52 (1 H, dt, *J* = 17.0, 1.5 Hz, CH_AH_B=CH), 5.99 (1 H, ddd, *J* = 17.0, 10.5, 5.0 Hz,

CH_2=C*H*), 7.25–7.42 (5 H, m, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.5, 15.9, 46.6, 65.0, 69.9, 72.3, 75.8, 94.9, 101.8, 119.6, 127.6, 128.5, 128.7, 135.1, 137.9, 159.0 ppm. Anal. Calcd for $C_{20}H_{27}NO_4Si$: C, 64.31; H, 7.29; N, 3.75. Found: C, 64.28; H, 7.13; N, 3.71.

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(22) Spectral data of **19**: $[\alpha]_D^{26}$ +26.7 (*c* 0.55, $CHCl_3$). IR (NaCl, film): ν_{max} = 2956, 1755, 1705, 1621, 1497, 1386, 1212, 1086, 976, 887 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 (9 H, s, TMS), 1.37 (3 H, d, *J* = 6.0 Hz, C*H*$_3$), 1.77 (1 H, dd, *J* = 17.5, 4.5 Hz, C*H*$_A$H$_B$-C=O), 1.97 (3 H, s, Ac), 2.13 (3 H, s, Ac), 2.33 (1 H, dd, *J* = 17.6, 6.8 Hz, CH$_A$*H*$_B$-C=O), 3.54 (1 H, m, C*H*CH$_2$), 4.08 (1 H, d, *J* = 17.2 Hz, -C*H*$_A$H$_B$-Ph), 4.70 (1 H, q, *J* = 6.0 Hz, C*H*CH$_3$), 5.24 (1 H, d, *J* = 5.6 Hz, CH-C*H*OAc), 5.24 (1 H, d, *J* = 17.2 Hz, CH$_A$*H*$_B$-Ph), 6.04 (1 H, d, *J* = 1.6 Hz, C=C-C*H*-OAc), 7.41–7.24 (5 H, m, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.6, 17.5, 20.3, 20.4, 38.9, 47.2, 48.5, 73.4, 74.9, 76.8, 77.8, 126.2, 128.1, 129.2, 137.1, 144.7, 158.2, 168.9, 169.1, 181.7, 211.2 ppm. HRMS (FAB$^+$): *m/z* calcd for $C_{25}H_{32}NO_7Si$ [M + H]: 486.1948; found: 486.1930.

(23) Another fraction contained an inseparable mixture of two minor products, whose structures have not been elucidated.