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Synthetic approach to tricyclic β-lactams using metathesis and Diels–Alder reactions

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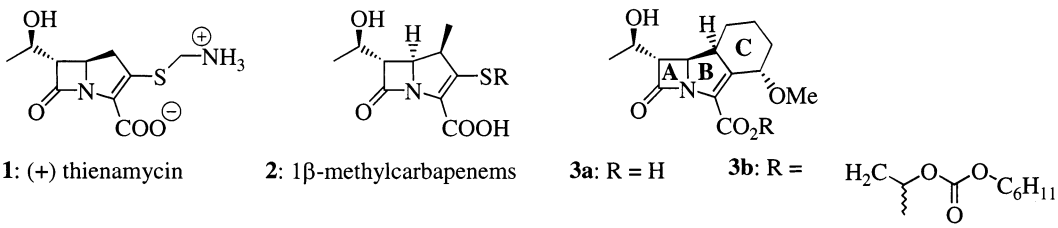
Abstract—A family of functionalised tribactams has been prepared using a new approach. The two main steps are an intramolecular metathesis reaction and a Diels–Alder cyclisation.

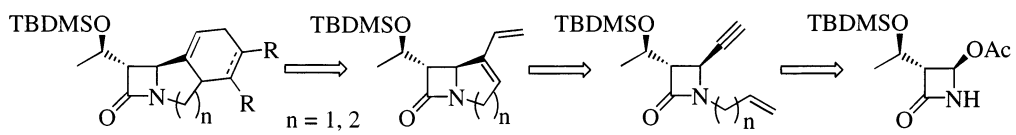
Since the discovery by the Merck group in the early 1980s of (+)-thienamycin **1**,[1] a natural fungal metabolite, the carbapenems and, more recently, the 1β-methylcarbapenems **2**,[2] have attracted considerable attention as the more promising β-lactam antibiotics due to their chemical and metabolic stability as well as their potent antimicrobial activity. Various synthetic efforts have been initiated to construct the bicyclic skeleton of thienamycin and 1β-methylcarbapenems.[3] In the early 1990s, trinem antibiotics endowed with outstanding chemical and metabolic stability have been discovered by GlaxoWellcome.[4]

These tribactams have been the subject of considerable attention owing to their broad spectrum of antibacterial activity, resistance to β-lactamase, and stability to renal deshydropeptidase.[5] Currently, the (4*S*)-methoxytrinem sanfetrinem **3a** and its orally active ester pro-drug sanfetrinem cilexetel **3b** are in Phase II clinical trials (Scheme 1). Following the very promising results



1: (+) thienamycin **2**: 1β-methylcarbapenems **3a**: R = H **3b**: R =

Scheme 1.



9 **8** **6** **4**

Scheme 2.

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obtained with sanfetrinem, research programs have focused on the synthesis of other tricyclic β-lactams using different approaches. Central ring cyclisation was achieved by Wittig type reaction,[6] Michael addition[7] or by aldol condensation.[8] The tricyclic structure could also be obtained by simultaneous formation of B and C rings by Pauson–Khand[9] or intramolecular Diels–Alder[10] reactions.

Recently, we have established the efficiency of (π-allyl)palladium methodology for the construction of the five-membered ring of the methylcarbapenems.[11] In this paper, we wish now to report a new approach to tribactams as shown in Scheme 2. The first key step was an enyne metathesis reaction affording efficiently the B ring of **8**.[12] The second step was a Diels–Alder cyclisation giving the tricyclic compound **9**.

The desired protected acetylenic **5** was conveniently prepared by condensation of the anion of the trimethylsilylacetylene on the commercially available (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-[(*t*-butyldimethylsilanyl)-oxy)ethyl]-azetidin-2-one **4**[13] with complete retention of configuration in 76% yield (Scheme 3). The azetidinone **5** was alkylated by allyl bromide (**6a**) or 4-bromo-but-1-ene (**6b**) using phase transfer conditions in good yields.

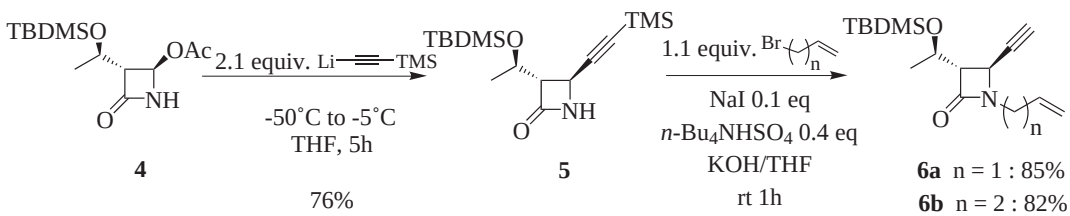
The first attempt of cyclisation was carried out with the precursor **6b** and 5% Grubbs catalyst **7** in dichloromethane, reflux, 4 hours, with a 0.1 M concentration. The diene **8b** was isolated in 80% yield (Scheme 4).[14] However, the cyclisation attempted with the β-lactam **6a** proved to be more difficult; under the same conditions, no cyclised product was observed and only 22% of the homo-metathesis product was isolated.[15] We carried out the reaction under higher dilution (0.003 M) and the bicyclic product **8a** was isolated in a non-optimised 29% yield.[16]

In the second step, the third ring was formed by Diels–Alder reaction. The reaction conditions have been determined with diene **8b** bearing the six-membered ring. The best conversion was obtained when the reaction was conducted in dichloromethane in a sealed tube at 80°C over a period of 48 hours (Scheme 5). Thus, the tricyclic 4,6,6-β-lactam **9b** was obtained starting from the dimethylacetylenedicarboxylate in 59% yield as two separable diastereomers in a 56:44 ratio (entry 1, Table 1).

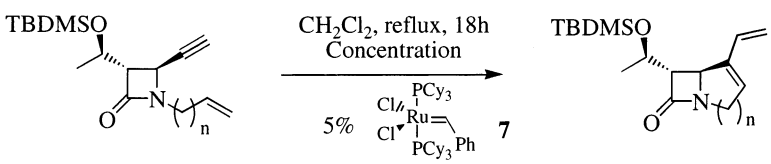
Under the same conditions, diene **8a** was engaged in Diels–Alder reactions with various dienophiles.[17] The results are represented in Table 1.

As for diene **8b**, the dimethylacetylenedicarboxylate gave two diastereomers but these were inseparable (entry 2, Table 1). We also tested other dienophiles like *N*-phenylmaleimide, maleimide or tetracyanoethylene in the Diels–Alder reaction as shown in Table 1. The adducts were isolated as single diastereomers in moderate yield. The structure of the tetracyclic compound **9a2** has been established by NOE NMR experiment.[18] Molecular modelling[19] of the diene bearing the five-membered ring **8a** showed that the two rings were displaying a 118° dihedric angle, thus confirming that the likely *endo* approach of the bulky dienophile on this diene had occurred on the less hindered face.

In summary, we have established a new route to tribactams using a metathesis/Diels–Alder sequence. The two B and C rings were formed in 85 and 45% yield, respectively. Application of this methodology to the preparation of functionalised tribactams is currently under investigation.

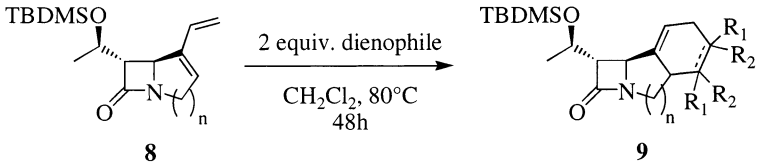


Scheme 3.



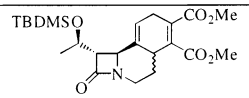
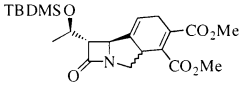
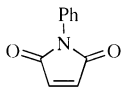
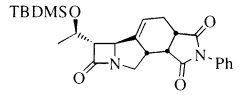
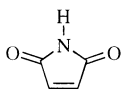
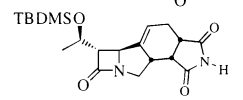
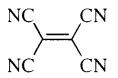
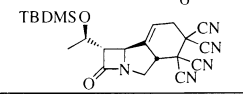
Starting material	Concentration	Product	Yield
6a, n = 1	0.003 M	**8a**	29%
6b, n = 2	0.1 M	**8b**	80%

Scheme 4.



Scheme 5.

Table 1. Diels–Alder cyclisations

Entry	Starting material	Dienophile	Product	Yield[(a)]
1	**8b** n = 2	MeO_2C—≡—CO_2Me	**9b** 	59%
2	**8a** n = 1	MeO_2C—≡—CO_2Me	**9a1** 	47%
3	**8a** n = 1		**9a2** 	44%
4	**8a** n = 1		**9a3** 	41%
5	**8a** n = 1		**9a4** 	49%

(a): isolated yields

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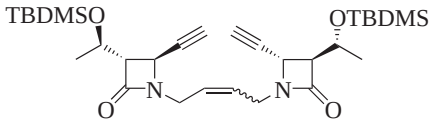
14. Previous attempts with terminal alkynes did not give the desired cyclisation, see: Ref. 12c.

15. 22% of the cross-metathesis product was isolated as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.11 (s, 12H), 0.89 (s, 18H), 1.24 (d, 6H, $J=6.3$ Hz), 2.47 (d, 2H, $J=2.1$ Hz), 3.23 (m, 2H), 3.66–3.74 (m, 2H), 3.98–4.07 (m, 2H), 4.24 (m, 4H), 5.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.5, 128.0, 80.2, 74.3, 65.9, 64.2, 41.9, 25.6, 22.2, 17.8, −4.5, −5.0; MS (CI, NH_3 m/z): 576 $(M+NH_4)^+$, 559 $(M+H)^+$.



16. Typical procedure for the enyne metathesis with degassed dichloromethane: Under an argon atmosphere, a three-necked flask was charged with dichloromethane (50 ml) and warmed to reflux. A solution of β-lactam **6a** (100 mg, 0.34 mmol) in dichloromethane (30 ml) and a solution of Grubbs catalyst (14 mg, 0.05 equiv., 0.017 mmol) in dichloromethane (30 ml) were added dropwise very slowly (8 hours) simultaneously at reflux. The solution was stirred 18 hours at reflux and the solvents were concentrated in vacuo. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90:10) gave 28.6 mg of **8a** (29%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.11 (s, 6H), 0.91 (s, 9H), 1.32 (d, 3H, $J=6.1$ Hz), 3.08 (dd, 2H, $J=7.3$ Hz, $J=2.1$ Hz), 3.61 (dd, 1H, $J=15$ Hz, $J=2.6$ Hz), 4.24 (dq, 1H, $J=7.2$ Hz, $J=6.3$ Hz), 4.42 (m, 2H), 5.21 (d, 1H, $J=10.7$ Hz), 5.41 (d, 1H, $J=17.6$ Hz), 5.85 (s, 1H), 6.52 (dd, 1H, $J=17$ Hz, $J=11$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.4, 142.0, 130.9, 129.7, 117.7, 67.2, 65.7, 60.7, 53.3, 25.9, 23.1, 18.1, −4.3, −4.5; IR (NaCl film): 1770 ($\nu_{C=O}$), 1258 (ν_{Si-CH_3}). Anal. calcd for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.35; H, 9.29; N, 4.69. $[\alpha]_D^{25}$ −51° (c 0.9, $CHCl_3$).
17. Typical procedure for the Diels–Alder cyclisation: Under an argon atmosphere, to a solution of diene **8a** (40 mg, 0.136 mmol) in dichloromethane (3 ml) was added *N*-phenylmaleimide (47 mg, 2 equiv., 0.27 mmol) in a tube. The tube was sealed and the solution was stirred for 24 hours at 80°C. The solvents were concentrated in vacuo and purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) gave 28 mg of the tetracyclic β-lactam **9a2** (44%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.25 (d, 3H, $J=6.2$ Hz), 2.25 (m, 1H), 2.90 (dd, 1H, $J=5.9$ Hz, $J=2.3$ Hz), 2.95 (dd, 1H, $J=16.4$ Hz, $J=6.5$ Hz), 3.08 (m, 1H), 3.31 (t, 1H, $J=7.5$ Hz), 3.44 (dd, 1H, $J=7.7$ Hz, $J=9.0$ Hz), 3.74 (dd, 1H, $J=12.6$ Hz, $J=8.5$ Hz), 4.10 (bs, 1H), 4.18 (m, 2H), 5.92 (m, 1H), 7.19 (m, 2H), 7.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1, 176.8, 176.2, 143.9, 131.5, 128.7, 129.1, 126.3, 119.6, 68.6, 65.8, 55.6, 46.4, 42.6, 41.1, 39.9, 30.1, 25.6, 22.6, 17.9, −4.4, −5.0; IR (KBr): 1747, 1697 ($\nu_{C=O}$), 1637 ($\nu_{C=C}$), 1250 (ν_{Si-CH_3}), 838, 776, 692 ($\nu_{aromatic}$); MS (CI, NH_3 m/z): 484 $(M+NH_4)^+$, 467 $(M+H)^+$, 409 $(M-C(CH_3)_3)^+$; $[\alpha]_D^{25}$ +24° (c 1.00, $CHCl_3$).
18. The NOE NMR experiment was recorded with a 400 MHz Bruker spectrometer with a 800 ms melting time.
19. The geometry of the products was optimised with the MOPAC module from the CS Chem3D program using the semiempirical method PM3. For the PM3 method, see: Stewart, J. P. P. *J. Comput. Chem.* **1989**, *10*, 209–221.