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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 7255–7259

Access to enantiopure polycyclic β-lactams by Diels–Alder reaction of novel inner-outer-ring 2-(silyloxy)dienes with a carbacepham skeleton

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Received 23 June 2004; revised 30 July 2004; accepted 4 August 2004
Available online 21 August 2004

Dedicated to the memory of Dr. Juan C. del Amo, a victim of the terrorist attack in Madrid, 11 March, 2004

Abstract—The synthesis of unprecedented inner-outer-ring 2-[*tert*-butyldimethylsilyloxy]dienes with a carbacepham structure in optically pure form and their totally π-facial *endo* selective Diels–Alder reactions to structurally novel polycyclic β-lactams is reported.
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β-Lactam antibiotics have occupied a central role in the vigil against bacterial infections over the past several decades.[1] The various families of β-lactam antibiotics differ in their spectrum of antibacterial activity and in their susceptibility to β-lactamase enzymes, which constitute the most common and growing form of antibacterial resistance.[2] The bacterial resistance to β-lactam antibiotics caused by their widespread use during the past decades, has motivated a growing interest in the preparation and biological evaluation of new types of β-lactams, which will overcome the defense mechanisms of the bacteria. Tricyclic β-lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases.[3] Besides, the ever-growing new applications of 2-azetidinones in fields ranging from enzyme inhibition[4] to the use of these products as starting materials to develop new synthetic methodologies,[5] has triggered a renewed interest in the building of new polycyclic β-lactam systems in an attempt to move away from the classical β-lactam antibiotic structures.[6]

On the other hand, the Diels–Alder reaction is one of the most powerful carbon–carbon bond-forming processes in both natural and non-natural products synthesis.[7] Between the wide variety of dienes to which it can be applied,[8] cyclic dienes in which one of the double bonds is *endo*-cyclic (inner-outer-ring dienes) are highly valuable for the construction of polycyclic structures.[9] Despite their high synthetic potential, inner-outer-ring mono- or dioxygenated dienes have found limited applications in Diels–Alder reactions.[10] Recently, we have established the efficiency of Lewis acid-promoted carbonyl-ene cyclizations for the stereoselective synthesis of carbacepham derivatives (type I).[11] We believe that these compounds with a hydroxyl-homoallyl moiety will prove to be useful for the preparation of novel inner-outer-ring 2-oxygenated dienes (type II), which serve as precursors of more complex fused polycyclic carbacepham (type III)[12] related to trinems (Scheme 1). We wish to report here a simple, efficient synthesis of novel enantiopure inner-outer-ring 2-[*tert*-butyldimethylsilyloxy]dienes with a carbacepham structure and their totally π-facial *endo* selective Diels–Alder reaction with *N*-methylmaleimide as an easy entry to structurally novel polycyclic carbacephams.

Starting materials, enantiopure 1-hydroxycarbacepham **1**, were stereoselectively prepared by treatment of the appropriate 2-azetidinone-tethered alkenylaldehydes with BF_3/Et_2O, using our methodology.[11] Our initial intention was to prepare the inner-outer diene derived from **1a** by elimination with DBU of its corresponding mesylate, following our previously reported method

Keywords: β-Lactam; 2-Azetidinone; Carbacepham; Diene; Diels–Alder cycloaddition.
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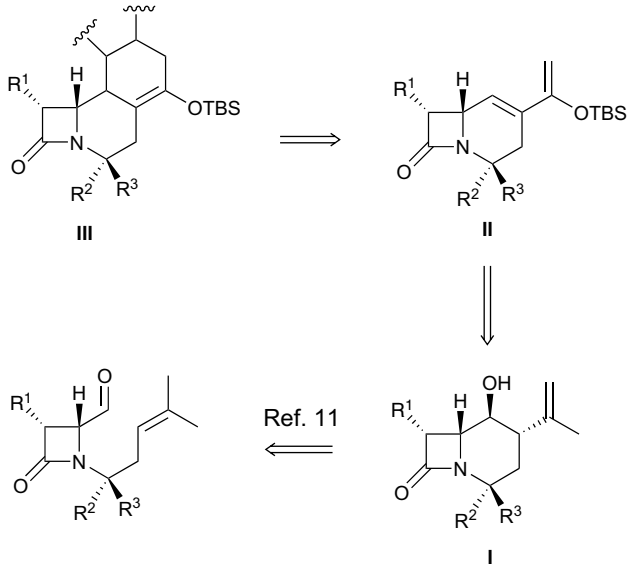
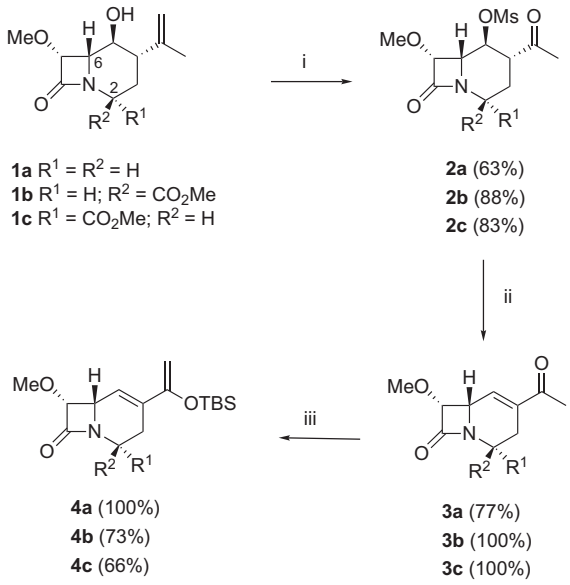
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.08.022



Scheme 1.



Scheme 2. Conditions: (i) (a) $MeSO_2Cl$, Et_3N, rt; (b) $RuCl_3$ (0.07 equiv)/$NaIO_4$ (4 equiv), $ClCH_2CH_2Cl/H_2O$ (5/4), rt. (ii) DBU (1 equiv), benzene, 30 min, rt. (iii) TBSTf (1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, 0 °C.

for the synthesis of monocyclic 2-azetidinone-tethered dienes.[13] However, under the described conditions (in refluxing toluene for 18 h) no elimination product was observed. The use of both longer reaction times at higher temperature and larger excess of base, was also unsuccessful, the starting mesylate being recovered unaltered. Due to the sensitivity of the carbacepham system toward stronger bases, we sought to develop mild reaction conditions, so as to minimize the destruction of the bicyclic system as well as to prevent the possible isomerization of the β-lactam ring. To overcome the limitation found in substrate **1a** and further increase the synthetic possibilities of the resulting elimination product, we used 2-acetylcarbacepham **2a** as starting material. This compound was prepared in good yield by oxidation of mesylate derivative of **1a** with the system $RuCl_3/NaIO_4$ in 1,2-dichloroethane/water as solvent at room temperature (Scheme 2).[14]

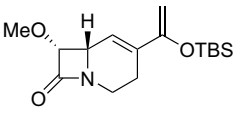
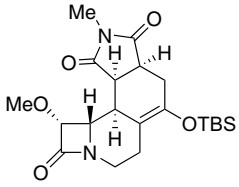
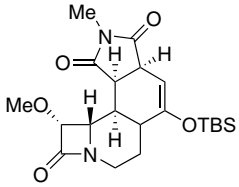
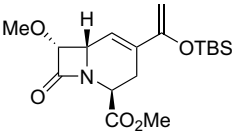
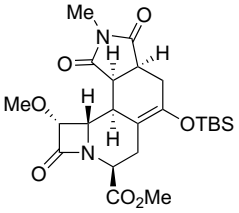
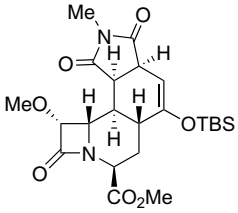
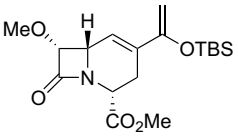
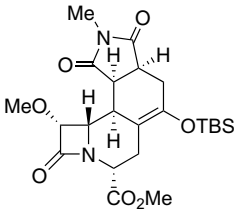
Gratifyingly, treatment of **2a** with one equivalent of DBU in benzene at room temperature for 25 min, smoothly gave enone **3a** in 77% yield. Following this procedure, other bicyclic enones **3b** and **3c** were obtained in good to excellent yields. Longer reaction times caused partial epimerization either at position C6 or C2, yielding mixtures of isomeric carbacephems. Thus, reaction of compound **2c** with DBU for 3 h took place with concomitant partial epimerization at position C2, giving a mixture of enones **3b** and **3c** in 35% and 65% yields, respectively, after purification by flash chromatography.

Also, compound **2a** gave an equimolar mixture of **3a** and its corresponding epimer at C6 after 1 h at room temperature in the presence of one equivalent of base. Having prepared the diene precursors **3** we then explored their transformation into the corresponding 2-silyloxy dienes **4**, which was easily achieved by reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of Et_3N in dichloromethane as solvent at 0 °C. Pure compounds **4** were obtained after column chromatography of their corresponding crude reaction mixtures on silica gel deactivated with Et_3N.[15]

With the basic methodology for the synthesis of activated bicyclic inner-outer-ring dienes **4** secure, our attention was turned to the study of their Diels–Alder reactions with *N*-methylmaleimide, which was selected as the reagent of choice. Table 1 summarizes our results for the different dienes **4** tested. Reaction of diene **4a** proceeded smoothly to stereoselectively provide tetracyclic carbacephams **5a** in very good yield as pure products by heating at 145 °C in a sealed tube for 3 h. Interestingly, when a solution of compound **5a** in deuterated chloroform was allowed to stand at room temperature for 1 h the isomeric tetracyclic carbacepham **6a** was smoothly obtained in nearly quantitative yield (^{1}H NMR monitoring). Formation of compound **6a** from **5a** is the result of an 1,3 migration of hydrogen, probably favored by acidic traces present in the monitoring solvent. In fact, when this ^{1}H NMR analysis was made in C_6D_6 as solvent, no transformation was observed, and the only detected signals were those of compound **5**.

We next explored reactions of more functionalized dienes **4b** and **4c**, with an extra methoxycarbonyl group on position C2. Because a carboxy group contiguous to the lactam nitrogen is a prerequisite for biological activity, the above substrates are of particular interest. Reaction of **4b** afforded an easily separable mixture of isomeric tetracyclic carbacephams **5b** and **6b**,[16] which were obtained in 26% and 37% yield, respectively, as pure products after chromatography. In this case, compound **5b** was stable in solution of deuterated chloroform

Table 1. Diels-Alder adducts **5** and **6** obtained from carbacephamic dienes **4** and *N*-methylmaleimide[a]

Entry	Starting diene	*t* (h)	Product (yield, %)[b]
1	 **4a**	3	 **5a** (82%) $\xrightarrow[1h, RT]{DCCl_3}$  **6a** (100%)
2	 **4b**	18	 **5b** (26%) +  **6b** (37%)
3	 **4c**	12	 **5c** (91%)

[a] Toluene, sealed tube, 145 °C.

[b] All new compounds described herein were fully characterized by spectroscopic methods and microanalysis and/or HRMS. All yields refer to chromatographed, pure (NMR, TLC) compounds.

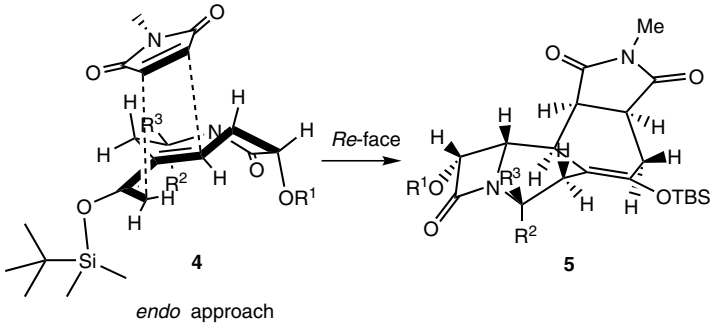


Figure 1. Proposed model for Diels–Alder cycloadditions of inner-outer-ring dienes **4** with *N*-methylmaleimide.

after several days at room temperature. No other attempts were made to transform adduct **5b** into its isomer **6b**. Finally, compound **4c** gave cycloadduct **5c** in excellent 91% yield as pure product, without any detectable isomerization product. The polycyclic structure (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **5** and **6** were established by NMR mono- and two-dimensional techniques.

The stereochemical outcome in the present intermolecular Diels–Alder cycloadditions of inner-outer-ring dienes **4** with *N*-methylmaleimide, leading exclusively to *endo* polycyclic carbacephams **5** and **6** can be rationalized through the transition state model depicted in Figure 1, involving a selective attack of the dienophile on the *Re* face of the bicyclic structure. In all cases the π-facial selectivity seems to be controlled by the C6 stereogenic center in the bicyclic diene.

In conclusion, we have demonstrated the utility of the reported methodology for the facile and diastereoselective elaboration of enantiopure polycyclic β-lactam systems relevant to the synthesis of novel carbacephem-type antibiotics. The synthetic potential of the novel inner-outer-ring silyloxydienes with a carbacepham

skeleton in Diels–Alder reactions with different dienophiles are currently under investigation and further aspects of this chemistry will be reported in due course.

Acknowledgements

We are grateful to the DGI (MCYT-Spain) for financial support of this research (Project BQU2003-07793-C02-01). C.R.-R. thanks the DGI (CEC-Comunidad de Madrid-Spain) for a predoctoral grant. R.M.M. thanks the MECD for a studentship ('beca de colaboración').

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14. Yang, D.; Zhang, Ch. *J. Org. Chem.* **2001**, *66*, 4814.
15. Representative experimental procedure for the synthesis of 2-(silyloxy)dienes **4**: *tert*-Butyldimethylsilyl trifluoromethane-sulfonate (1.2 mmol) was added dropwise to a solution of the corresponding enone **3** (1 mmol) and Et_3N, under argon and cooled at 0 °C in anhydrous dichloromethane (5 mL). The reaction mixture was stirred for 2 h. The mixture was washed with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel deactivated with Et_3N and eluting with EtOAc/hexanes gave analytically pure compounds **4**. Selected data for 2-(silyloxy)diene (−)-**4a**. From 23 mg (0.12 mmol) of enone (+)-**3a**, 36 mg (100%) of compound (+)-**4a** was obtained as a colorless oil. $[\alpha]_D = +61.9$ (*c* 1.0, C_6H_6). ^1H NMR (C_6D_6): 0.24 (s, 3H), 0.25 (s, 3H), 1.09 (s, 9H), 1.74 (ddt, 1H, $J = 1.4, 2.4, 15.0$ Hz), 2.28 (m, 1H), 2.39 (m, 1H), 3.29 (s, 3H), 3.66 (dd, 1H, $J = 2.3, 4.7$ Hz), 3.78 (dd, 1H, $J = 6.0, 12.5$ Hz), 4.23 (d, 1H, $J = 4.7$ Hz), 4.33 (s, 1H), 4.39 (s, 1H), 6.48 (s, 1H). ^{13}C NMR (C_6D_6): δ 170.1, 155.7, 134.6, 120.7, 91.9, 85.9, 58.3, 51.7, 35.9, 26.0, 23.5, 18.4, −4.5, −4.8. IR ($CHCl_3$, cm^{-1}): *v* 1741. MS (CI), *m/z*: 309 (M^+, 8), 252 (M^+-57, 11), 73 (100).
16. Selected data for compound **5b**: Colorless oil. $[\alpha]_D = +8.4$ (*c* 0.5, C_6H_6). ^1H NMR (C_6D_6): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.93 (s, 9H), 1.13 (ddd, 1H, $J = 6.6, 12.6, 13.6$ Hz), 1.93 (dt, 1H, $J = 4.7, 10.9$ Hz), 2.34 (tq, 1H, $J = 2.3, 11.9$ Hz), 2.66 (s, 3H), 2.71 (m, 2H), 2.96 (ddd, 1H, $J = 2.7, 3.5, 7.7$ Hz), 3.26 (s, 3H), 3.42 (s, 3H), 4.29 (d, 1H, $J = 4.8$ Hz), 4.67 (bd, 1H, $J = 6.0$ Hz), 4.99 (dd, 1H, $J = 2.1, 3.5$ Hz), 5.12 (dd, 1H, $J = 4.8, 10.7$ Hz). ^{13}C NMR (C_6D_6): δ 177.0, 176.9, 170.1, 167.2, 153.5, 100.3, 85.1, 58.5, 52.1, 51.8, 49.6, 41.5, 38.9, 37.8, 33.7, 30.0, 25.6, 24.1, 18.2, −4.6, −5.1. IR ($CHCl_3$, cm^{-1}): *v* 1743, 1703. MS (EI), *m/z*: 478 (M+, 2), 421 (M^+-57, 19), 364 (M^+-115, 45), 73 (100). (Anal. Calcd for $C_{23}H_{34}N_2O_7Si$: C, 57.72; H, 7.16; N, 5.85. Found: C, 57.79; H, 7.22; N, 5.95). Compound **6b**: colorless oil. $[\alpha]_D = +38.5$ (*c* 0.5, C_6H_6). ^1H NMR (C_6D_6): δ 0.02 (s, 3H), 0.15 (s, 3H), 0.98 (s, 9H), 1.80 (m, 1H), 2.26 (bt, 1H, $J = 14.5$ Hz), 2.34 (t, 1H, $J = 7.6$ Hz), 2.58 (bd, 1H, $J = 16.5$ Hz), 2.63 (s, 3H), 2.74 (m, 2H), 3.28 (m, 1H), 3.31 (s, 3H), 3.44 (s, 3H), 4.22

(dd, 1H, $J = 5.3$, 12.2 Hz), 4.39 (d, 1H, $J = 4.5$ Hz), 5.01 (dd, 1H, $J = 4.5$, 10.2 Hz). ^{13}C NMR (C_6D_6): δ 178.2, 177.2, 170.5, 168.7, 145.3, 108.9, 83.9, 58.6, 51.9, 51.5, 51.0, 40.6, 40.2, 35.7, 29.8, 25.6, 24.9, 24.5, 18.1, −4.2, −4.4. IR ($CHCl_3$, cm^{-1}): ν 1744, 1700. MS (EI), *m*/*z*: 478 (M+, 6), 463 (M^+-15, 3), 421 (M^+-57, 100). (Anal. Calcd for $C_{23}H_{34}N_2O_7Si$: C, 57.72; H, 7.16; N, 5.85. Found: C, 57.82; H, 7.09; N, 5.94).