Practical Access to Carbacephem Intermediates via Asymmetric [2 + 2] Ketene−Imine Cycloaddition

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Since the discovery and structural elucidation of penicillin G and the closely related cephalosporin C there have been considerable efforts to find new drugs with a broader degree of antibacterial activity, greater chemical stability, and better pharmacokinetic profile.[1] Within this context, carbacephems, in which the sulfur atom at position-1 is replaced by methylene, have been shown to have comparable activity with the corresponding cephalosporins.[2] An illustrative example is lorabide or loracarbef **1** (Figure 1), which possesses a spectrum of biological activity similar to ceclor **2** but is substantially superior in chemical stability.[3] At present, this family of compounds is not directly accessible via either fermentation processes or structural modifications of naturally occurring β-lactam antibiotics.[4] The literature pertaining the synthesis of carbacephems[5] suggests that the Dieckmann cyclization of **3** generally becomes the method of choice for forming the key six-membered ring [6] although the rhodium acetate mediated carbene insertion into the N−H bond of the β-lactam **4** has also been used to some extent.[7,8] On the other hand, there are now a variety of

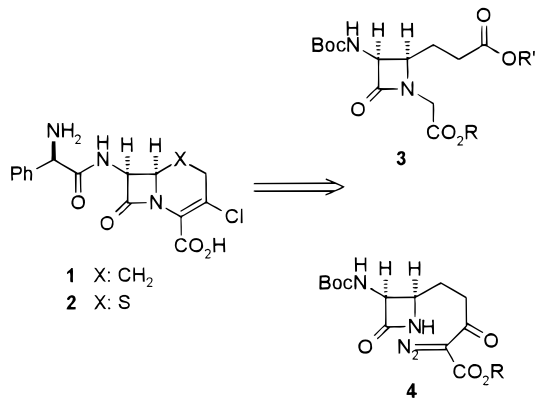

Figure 1.

suitable methods for the synthesis of monocyclic β-lactams.[9] These include the hydroxamate methodology,[10] the metalloester enolate−imine condensation,[11] the chromium carbene−imine reaction,[12] and the [2 + 2] cycloaddition of ketenes with imines.[13] In particular, the last provides useful and economical access to 3-amino β-lactams, mainly due to the ready availability of ketenes generated by dehydrohalogenation of their corresponding acid chlorides and a tertiary organic base. A remarkable example is the aminoketene of Evans−Sjögren,[14] gener-

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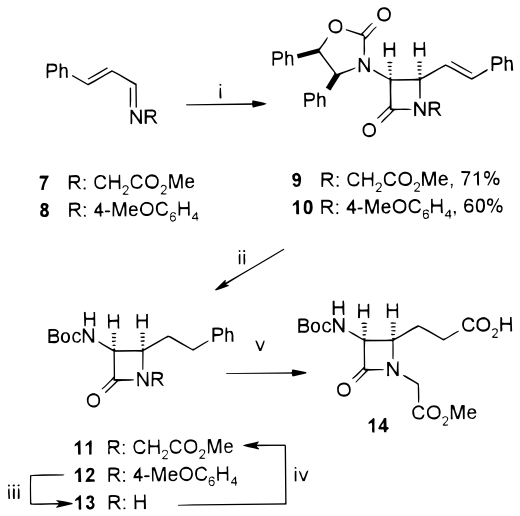
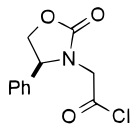
Scheme 1[a]

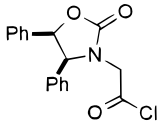


[a] Reagents and conditions: (i) **6**, NEt_3, CH_2Cl_2, −78 °C → rt; (ii) H_2, $Pd(OH)_2$, $(Boc)_2O$, THF, rt; 120 psi; 84% for **11**; 80% for **12**; (iii) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0 °C, 82%; (iv) $CsCO_3$, CH_3CN, $BrCH_2CO_2CH_3$, rt, 24 h, 40% (not optimized); (v) H_5IO_6, $CCl_4-CH_3CN-H_2O$; 78%.

ated from the oxazolidinylacetic acid chloride **5** and triethylamine, that upon treatment with imines provides 3-amino β-lactams in good yields and excellent diastereoselectivity, typically ≥96% de. Various syntheses of



5



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both **3** and **4** make use of this reaction.[6b,7a,b,15] In these cases, two methods, a dissolving metal reduction[7] and a treatment with trimethylsilyl iodide,[16] have been reported for the removal of the oxazolidinyl moiety from the resulting cycloadducts. In this paper, we report a complementary simple procedure for the preparation of carbacephem building blocks that is based on the use of the oxazolidinylacetic acid chloride **6**,[17] as cycloaddition reagent element, which leads to β-lactams on which deprotection of the amino function can be effected under hydrogenolytic conditions.

The β-lactams **9** and **10**, whose phenyl ring at position C_4 could easily be transformed into the required carboxyl moiety,[18] were selected for the illustration of our method (Scheme 1). Both β-lactam products were prepared by standard [2 + 2] cycloaddition reaction of the aminoketene derived from **6**, in the presence of triethylamine, to imines **7** and **8** derived from the commercially available cinnamaldehyde. As expected, the cycloaddition proceeded in both cases with remarkable diastereoselectivity, typically ≥97 de. Exposure of β-lactam **9** to hydrogen over Perlman's catalyst led to the removal of the oxazolidinone ring together with the reduction of the double bond. The resulting 3-amino β-lactam was then isolated as the *N*-Boc derivative **11** in 70% yield. In terms of chemical yield and simplicity, it was found to be more convenient to perform the hydrogenation step in the presence of di-*tert*-butyl carbonate. This allowed the β-lactam **11** to be obtained in a single-pot operation in 84% isolated yield after column chromatography. Likewise, the β-lactam **10** upon treatment with H_2 under these reaction conditions gave the *N*-Boc β-lactam **12** in 80% yield. It is interesting to note that this β-lactam product could not be obtained under standard Birch-type conditions.[7] Therefore, the method reported here appears to be complementary to the previously reported procedures,[7,10] and in view of its simplicity, it also seems to be potentially applicable for scale-up.

Confirmation of the configuration of the products was established by conversion of **12** into **13** according to the Kronenthal procedure[19] and subsequent N-alkylation of **13** with methylbromoacetate. The resulting product **11** was identical in all respects to that obtained from **9**. The cis configuration of these adducts was determined on the basis of coupling constants between protons at C_3 and C_4 and the assigned relative configuration by assuming the same stereochemical outcome as that observed for cycloadditions involving the aminoketene derived from the acid chloride **5**. We also converted compound **11** into intermediate **14** of the synthesis of antibiotic loracarbef. The phenyl ring in **11** was oxidatively transformed into the carboxyl group according to the procedure of Sharpless,[20] modified by Martin.[21] Compound **14** was obtained in 65% yield and isolated as a dicyclohexylammonium salt.

In summary, the method described here provides an important β-lactam intermediate in a concise and practical way that facilitates the development of carbacephems from academic and industrial standpoints. From these results, it is expected that other attractive targets should also be efficiently prepared by this route.

Experimental Section

Melting points were determined with a capillary apparatus and are uncorrected. ^1H nuclear magnetic resonance (300 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CDCl_3$ δH (7.26 ppm) and $CDCl_3$ δC (77.0 ppm) as internal standards, respectively. Optical rotations were measured at 25 ± 0.2 °C in methylene chloride or methanol unless otherwise stated. Flash chromatography was executed with Merck Kiesegel 60 (230−400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potas-

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sium carbonate, and distilled. Commercially available compounds were used without further purification. Compound **6** was prepared as described.[17d]

***cis*-(3*S*,4*R*)-3-[(4*S*,5*R*)]-4,5-Diphenyl-2-oxooxazolidin-3-yl]-1-[(methoxycarbonyl)methyl]-4-styrylazetidin-2-one (9).** Triethylamine (1.45 mL, 16.6 mmol) was added at −78 °C to a solution of the acid chloride **6** (3.47 g, 11 mmol) in dry methylene chloride (50 mL). After 20 min, a solution of the imine **7** (2.48 g, 12.2 mmol) in dry toluene (50 mL) was added dropwise at the same temperature. The cooling bath was removed, and the resulting mixture was stirred,under nitrogen atmosphere at 0 °C for 2 h. Then the reaction mixture was successively washed with water (100 mL), 1 N HCl (50 mL), and a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced presure to afford a crude material that was purified by flash column chromatography (silica gel, 230−400 mesh, methylene chloride and methylene chloride/ethyl acetate 10:1 as eluants) to give the desired product: 71% (3.8 g); mp 194−196 °C; $[\alpha]^{25}_D = +77.6$ ($c = 1.0$, CH_2Cl_2); IR (NaCl) ν 1760 (C═O), 1740 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.45−6.89 (m, 15H), 6.75 (d, 1H, $J = 16.0$ Hz), 6.37 (dd, 1H, $J = 8.9$, 16.0 Hz), 5.82 (d, 1H, $J = 8.4$ Hz), 5.06 (d, 1H, $J = 8.4$ Hz), 4.66 (dd, 1H, $J = 5.1$, 8.9 Hz), 4.58 (d, 1H, $J = 5.1$ Hz), 4.45 (d, 1H, $J = 18.2$ Hz), 3.70 (s, 3H), 3.65 (d, 1H, $J = 18.2$ Hz); ^{13}C NMR ($CDCl_3$) 168.3, 164.1, 157.4, 137.9, 135.4, 133.9, 133.1, 128.6, 126.7, 125.9, 122.4, 80.1, 65.4, 63.8, 62.0, 52.2, 41.2. Anal. Calcd for $C_{29}H_{26}N_2O_5$ (482.54): C, 72.18; H, 5.43; N, 5.80. Found: C, 72.33; H, 5.14; N, 5.78.

***cis*-(3*S*,4*R*)-3-[(4*S*,5*R*)-4,5-Diphenyl-2-oxooxazolidin-3-yl]-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (10).** The title compound was prepared from the acid chloride **6** (6.3 g, 20 mmol), the imine **8** (4.26 g, 18 mmol), and triethylamine (41 mmol) following the above procedure. The resulting crude was washed with ethyl acetate and the solid residue recrystallized from ethyl acetate: yield 60%; mp 262−264 °C; $[\alpha]^{25}_D = +55.9$ ($c = 1.0$, CH_2Cl_2); IR (NaCl) ν 1743 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.44−6.89 (m, 19H, arom), 6.82 (d, 1H, $J = 16.3$ Hz), 6.41 (dd, 1H, $J = 8.8$, 16.3 Hz), 5.84 (d, 1H, $J = 8.6$ Hz), 5.14 (d, 1H, $J = 8.6$ Hz), 4.83 (dd, 1H, $J = 5.3$, 8.8 Hz), 4.64 (d, 1H, $J = 5.3$ Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$) 161.2, 156.9, 137.7, 136.2, 134.7, 134.0, 131.9, 129.4, 129.2, 129.1, 128.8, 128.7, 128.5, 127.6, 126.7, 124.6, 119.1, 114.9, 81.0, 66.1, 63.6, 62.18, 56.11. Anal. Calcd for $C_{33}H_{28}N_2O_4$ (516.59): C, 76.72; H, 5.46; N, 5.42. Found: C, 76.91; H, 5.37; N, 5.41.

General Procedure for Simultaneous Hydrogenolysis and *N*-Boc Protection of β-Lactams 9 and 10. Pearlman's catalyst (Acros, 200 mg) and di-*tert*-butyl dicarbonate (0.65 g, 3 mmol) were added successively to a solution of the corresponding 3-oxazolidinyl-β-lactam (1 mmol) in THF (30 mL). The resulting mixture was stirred at room temperature under a hydrogen atmosphere (120 psi) for 48 h. Then the mixture was filtered through Celite, and after evaporation of the filtrate under reduced pressure, the resulting crude was purified by chromatography to give the desired product.

***cis*-(3*S*,4*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-phenylethyl)-1-[(methoxycarbonyl)methyl]azetidin-2-one (11).** The title compound was prepared from **9** (0.48 g, 1 mmol) following the general procedure in a yield of 84%. The white solid was purified by flash chromatography (silica gel, 230−400 mesh, methylene chloride and methylene chloride/ethyl acetate 10:1): mp 100−103 °C; $[\alpha]^{25}_D = +4.8$ ($c = 1.0$, CH_2Cl_2); IR (KBr) ν 3339 (NH), 1746 (C═O), 1729 (C═O), 1685 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) 7.32−7.16 (m, 5H), 5.45 (d, 1H, $J = 8.7$ Hz), 5.16 (dd, 1H, $J = 8.7$, 5.0 Hz), 4.09 (d, 1H, $J = 18.1$ Hz), 3.93 (dt, 1H, $J = 8.0$, 5.0 Hz), 3.72 (s, 3H), 3.72 (d, 1H, $J = 18.1$ Hz), 2.6 (m, 2H), 1.9 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) 168.2, 167.1, 155.0, 140.8, 128.4, 128.3, 128.2, 128.1, 126.1, 80.3, 59.9, 59.0, 52.3, 41.6, 31.9, 30.5, 28.1. Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.43): C, 62.96; H, 7.23; N, 7.72. Found: C, 63.04; H, 7.11; N, 7.68.

***cis*-(3*S*,4*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-phenylethyl)-1-(4-methoxyphenyl)azetidin -2-one (12).** The title compound was prepared from **10** (0.52 g, 1 mmol) following the general procedure in a yield of 80%. The white solid was purified by flash chromatography (silica gel, 230−400 mesh, methylene chloride and methylene chloride/ethyl acetate 10:1): mp 184−186 °C (ethanol); $[\alpha]^{25}_D = -10.6$ ($c = 1.0$, CH_2Cl_2); IR (KBr) ν 3335, 1740 (C═O), 1633 cm^{-1} (C═O), ^1H NMR ($CDCl_3$) 7.42−6.89 (m, 9H), 5.68 (d, 1H, $J = 8.4$ Hz), 5.31 (dd, 1H, $J = 4.9$, 8.4 Hz), 4.25 (m, 1H), 3.84 (s, 3H), 2.72 (m, 2H), 2.31 (m, 1H), 1.96 (m, 1H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$) 164.1, 156.3, 140.7, 128.5, 128.2, 126.1, 118.7, 114.3, 80.5, 58.9, 57.2, 55.4, 31.5, 29.6, 28.2. Anal. Calcd for $C_{23}H_{28}N_2O_4$ (396.48): C, 69.67; H, 7.11; N, 7.06. Found: C, 69.65; H, 6.95; N, 7.06.

Preparation of the Loracarbef Intermediate 14. To a mixture of the β-lactam **11** (0.31 g, 0.85 mmol) in carbon tetrachloride (5 mL), acetonitrile (5 mL), and water (7.5 mL) was added at room-temperature periodic acid (2.75 g, 12 mmol). The biphasic mixture was stirred until both phases became clear, and ruthenium trichloride hydrate (350 mg, 0.17 mmol) was added. Stirring was continued until no starting material was detected by TLC (4 h). The reaction mixture was cooled to 0 °C, and diethyl ether (50 mL) was added with vigorous stirring for 10 min. The organic phase was separated and the aqueous layer extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried, filtered, and concentrated. The residue was dissolved in ethyl acetate (10 mL), dicyclohexylamine (0.121 g, 0.67 mmol) was added, and the resulting mixture was stirred at room temperature overnight. The resulting crystals were filtered, and then a biphasic mixture of ethyl acetate (10 mL) and a solution of $KHSO_4$ (0.14 g, 1 mmol) in water (10 mL) was added. The mixture was stirred until the dicyclohexylammonium salt was completely dissolved. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the organic phases were dried and evaporated under reduced presure to give the desired product **14**: yield 65%; mp 128−130 °C; $[\alpha]^{25}_D = +8.0$ ($c = 1.0$, MeOH); IR (KBr) ν 3334 (NH), 1761 (C═O), 1748 (C═O), 1677 cm^{-1} (NHCOO); ^1H NMR ($CDCl_3$) 5.43 (d, 1H, $J = 8.1$ Hz), 5.11 (dd, 1H, $J = 8.01$, 4.7 Hz), 4.15 (d, 1H, $J = 18.1$ Hz), 3.95 (dt, 1H, $J = 4.7$, 8.8 Hz), 3.87 (d, 1H, $J = 18.1$ Hz), 3.74 (s, 3H), 2.34 (m, 2H), 2.00 (m, 1H), 1.81 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) 176.7, 168.2, 167.3, 155.3, 80.7, 59.8, 58.7, 52.5, 41.4, 29.6, 28.1, 23.3. Anal. Calcd for $C_{14}H_{22}N_2O_7$ (330.33): C, 50.90; H, 6.71; N, 8.47. Found: C, 50.79; H, 6.58; N, 8.57.

***cis*-(3*S*,4*R*)-3-[(*tert*-Butoxycarbonyl)amino]-4-(2-phenylethyl)azetidin-2-one (13).** A solution of ceric ammonium nitrate (CAN) (1.54 g, 2.8 mmol) in water (30 mL) was added to a mixture of β-lactam **12** (0.37 g, 0.94 mmol) in acetonitrile (50 mL) cooled at 0 °C. The reaction mixture was stirred for 45 min and then was diluted with water (200 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed with 5% sodium bicarbonate (50 mL), and the aqueous phase was re-extracted with ethyl acetate (50 mL). The combinated organic phases were washed with 10% sodium sulfite (30 mL), 5% sodium bicarbonate (30 mL), and brine (30 mL). The organic layer was dried, the solvent was evaporated under reduced pressure, and the product was purified by flash chromatography (silica gel 230−400 mesh; CH_2Cl_2/EtAcO 10:1 and then CH_2Cl_2/EtAcO 2:1) to obtain the desired product: yield 82%; mp 130−132 °C (ethanol); $[\alpha]^{25}_D = +62.1$ ($c = 1.0$, CH_2Cl_2); IR (KBr) ν 3337 (NH), 1737 (C═O), 1685 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.30−7.15 (m, 5H), 6.33 (s, 1H), 5.46 (d, 1H, $J = 8.2$ Hz), 5.04 (dd, 1H, $J = 4.7$, 8.2 Hz), 3.76 (m, 1H), 2.63 (m, 2H), 1.78 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) 169.0, 155.9, 141.4, 129.1, 128.9, 126.7, 80.9, 60.7, 55.2, 33.0, 32.8, 28.8. Anal. Calcd for $C_{16}H_{22}N_2O_3$ (290.36): C, 66.18; H, 7.63; N, 9.64. Found: C, 66.24; H, 7.78; N, 9.53.

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Supporting Information Available: Representative ^1H and ^{13}C NMR spectra of compounds **9**, **11**, **12**, and **14** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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