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Catalytic Approaches to the Synthesis of β-Lactamase Inhibitors

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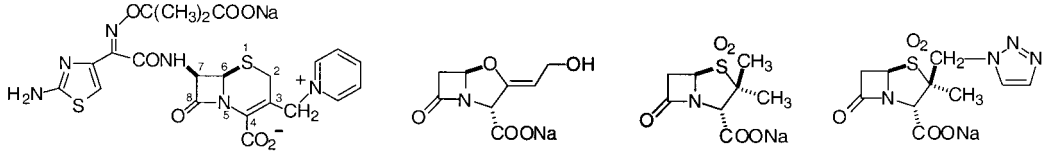
Abstract—Catalytic couplings were utilized to stereospecifically synthesize several 7*E*- and 7*Z*-alkylidenecephalosporins. Members of this class are known inhibitors of β-lactamase. Zinc/NH_4Cl reduction of dibromide **14** stereospecifically produced *E*-monobromide, **15**. In contrast, treatment of **14** with isopropylmagnesium bromide, followed by mild acid, stereospecifically produced *Z*-monobromide **27**. These reactions involve stable, intermediate α-(metalloalkylidene)-β-lactams. Monobromides **15** and **27** were stereospecifically coupled to organostannanes, or were converted to the corresponding organostannanes, **22** and **32**, which coupled with organohalides.

Introduction

Due to their excellent safety profile and broad spectrum, β-lactam antibiotics remain the most commonly prescribed antimicrobials. However, antibiotic-resistant strains are arising at an alarming rate. The most prevalent cause of bacterial resistance involves drug deactivation through a β-lactamase mediated process. The number of β-lactamases now exceeds 200.[1] Classes A, C, and D are serine hydrolases, while class B are zinc metalloenzymes. Historically, class A penicillinases have been the most clinically important. In the past decade, however, the incidence of class B and C-mediated infections has increased dramatically. Class B metalloenzymes are now responsible for resistance in a number of pathogenic bacteria including the *Klebsiella*, *Serratia*, *Pseudomonas*/*Stenotrophomonas* and *Bacteroides* genera. Multifocal outbreaks of class B metallo-β-lactamase-producing *Pseudomonas aeruginosa*, resistant to carbapenems and other broad-spectrum antibiotics, have been reported in Japanese hospitals.[2] Class C (AmpC) β-lactamase is now present in 10–50% of patients infected with *Citrobacter freundii*, *Enterobacter cloacae*, *Serratia marcescens*, and *P. aeruginosa*. Recently, plasmid-encoded class C β-lactamases[3] have been described in isolates of *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, and *Salmonella senftenberg*.[4]

Two approaches to overcoming the problem of lactamase-mediated resistance are: (a) designing antibiotics which are poor substrates for this enzyme, or (b) coadministration of an antibiotic and a β-lactamase inhibitor.[5] The former approach has produced third generation cephalosporins, such as ceftazidime (**1**) (Fig. 1), which incorporate sterically large oximino substituents at the 7-position. This approach is currently threatened by the high mutation rate of the lactamases. Some resistant strains now possess extended spectrum β-lactamases (ESBL's) capable of hydrolyzing these new cephalosporins.[6]

The second approach has also been successful.[7] The most commonly used commercial inhibitor is clavulanic acid (**2**), which is coadministered together with amoxicillin in the form of Augmentin®. Other inhibitors include sulbactam (**3**), which is coadministered with ampicillin in the form



1 2 3 4

Figure 1.

Keywords: tin and compounds; cephalosporins; penicillins; enzyme inhibitors.
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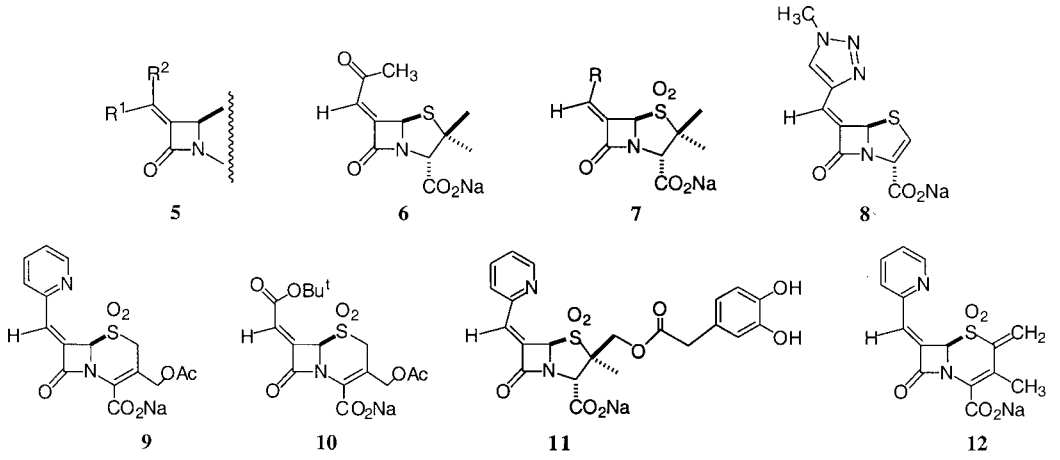


Figure 2.

of Unasyn® (injectable) or Sultamicillin® (oral), and tazobactam (**4**), which is coadministered with piperacillin in the form of Zosyn®. However, these inhibitors effectively target only the class A β-lactamases. Relative to the ESBL's, inhibitor resistant β-lactamases,[8] such as the inhibitor-resistant TEM-derived enzymes (IRT's) have spread less rapidly, possibly due to the fact that these enzymes have a reduced affinity for normal substrates (such as cephalothin).[7] Since clinically useful inactivators of either class B or class C enzymes are still nonexistent, there is a pressing need for wider spectrum inhibitors.

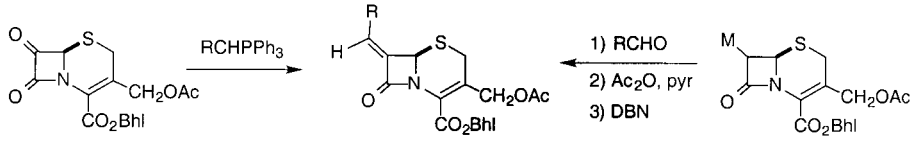
Our group has been involved in the synthesis and evaluation of new inactivators of these hydrolytic enzymes. Many of our compounds contain an α-alkylidene-β-lactam unit, **5** (Fig. 2). Historically, several potent β-lactamase inhibitors of this type have been reported, including Ro 15-1903 (**6**),[9] the 6-alkylidenepenicillin sulfones (**7**)[10,11] and the penem BRL 42715 (**8**).[12,13] We have discovered new inhibitors of the cephalosporin skeleton, including (**9**) and (**10**) which inactivate the class C and class A enzymes, respectively.[14] We have recently explored the effect of adding 2′-substituents on the 6-alkylidene penam sulfones, leading to the production of **11**, which exhibits excellent synergy (with piperacillin) in the treatment of gram negative organisms, including *Pseudomonas aeruginosa*.[15] Our synthetic studies have led to a new class of inhibitors of human leukocyte elastase (HLE),[16] an enzyme which is overactive in certain disease states, including emphysema and rheumatoid arthritis. Lastly, we have recently reported the effect of appending a 2′-methylidene to the 7-alkylidenecephalosporin sulfones, leading to the potent class C inhibitor **12**.[17]

Available synthetic methodology for the preparation of α-alkylidene-β-lactams includes two methods: (1) a Wittig reaction on the corresponding (penam or cephem-derived) α-oxo-β-lactam, or (2) a reaction of the α-metallated-β-lactam with an appropriate aldehyde or ketone, followed by elimination. In either case, the predominant (and, in many cases, selective) stereochemical geometry of the product alkene is *Z*. Although the aldol approach can be reasonably synthetically efficient for penams,[18,19] in both the cases of the penems[20] and the cephalosporins[21] the requisite anions are difficult to prepare, relatively unstable, and the yields usually poor (Scheme 1).

We desired a method for the rapid preparation of potential alkylidene inhibitors. Ideally, this would be achieved by utilizing a single, readily accessible, reactive, β-lactam-containing intermediate which could then be coupled with a commercially available collection of compounds in a stereocontrollable fashion. The Stille coupling[22] has already found utility in the preparation of 3-substituted cephems.[23] We recently reported its usefulness in the preparation of 7-[(*E*)-alkylidene]cephalosporins.[24] We would now like to present a thorough investigation of the potential for catalytic couplings to provide stereospecific access to members of the α-alkylidene-β-lactam family.

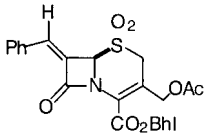
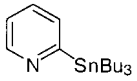
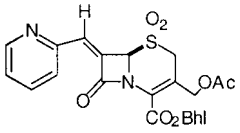
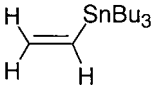
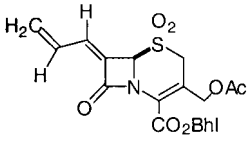
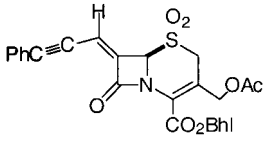
Results and Discussion

Our first objective was to generate stereospecific routes to both the 7*E*- and 7*Z*-bromomethylidenecephalosporins **15** and **27**. Dibromide **14**, which is readily prepared from 7-oxocephalosporanate **13**,[25] reacted with zinc/NH_4Cl to produce *E*-monobromide **15** in 83% yield.[14] This material was then coupled with representative organostannanes to yield the corresponding *E*-(substituted)alkylidenes, as shown in Table 1. The reaction was stereospecific, with retention of configuration at the 7′-position. However, it was complicated by a concurrent partial isomerization of



Scheme 1.

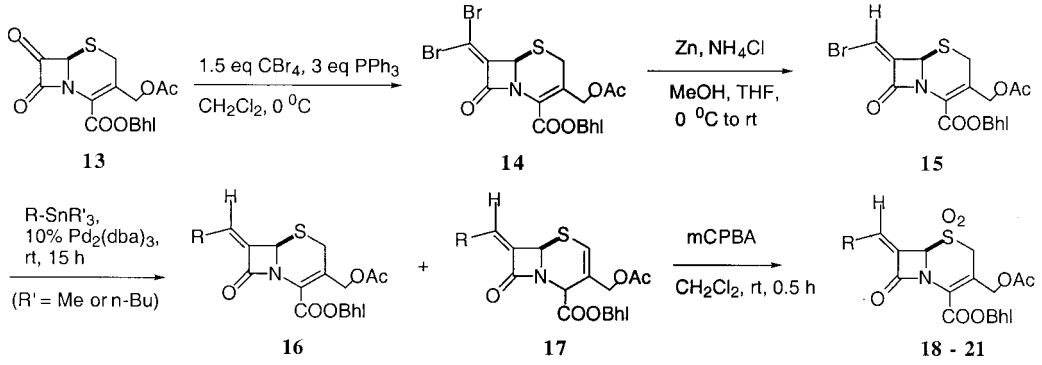
Table 1. Stille coupling of **15** with selected organostannanes, followed by oxidation

Entry	Stannane	Conditions	Product	Yield
1	Ph–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) mCPBA, CH_2Cl_2	 **18**	81%
2		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) mCPBA, CH_2Cl_2	 **19**	72%
3		(1) 10% $Pd_2(dba)_3$, DMF, rt, 10 h (2) mCPBA, CH_2Cl_2	 **20**	80%
4	Ph–C≡C–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) mCPBA, CH_2Cl_2	 **21**	76%

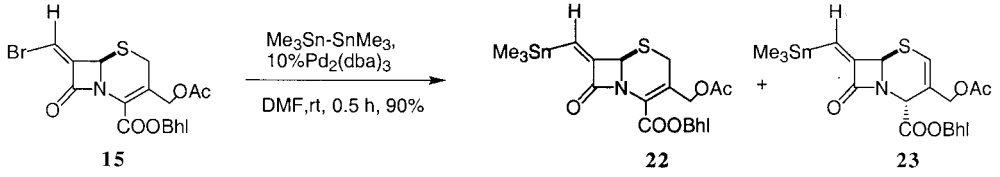
the dihydrothiazine double bond from the Δ-3,4 (cephalosporin numbering) to the Δ-2,3 position, forming a mixture of **16** and **17** as shown (Scheme 2). Fortunately, the desired β-lactamase inhibitors are sulfones and the product mixture is shifted quantitatively to the side of the Δ-3,4-isomer upon subsequent oxidation.

Treatment of the bromide **15** with hexamethylditin and Pd catalyst afforded an easily separable 3:1 mixture of the corresponding stannane **22** and its Δ-2,3 isomer **23**, respectively (Scheme 3). Bromide **15** could also be transformed into a similar mixture of vinylstannanes by the use of the Lipshutz higher order cuprate.[26,27] The product stannane **22** was coupled to selected organohalides as shown in Table 2. These two methods thus provide convenient routes to the previously unavailable 7*E*-alkylidenecephems.

Since nearly all reported inhibitors have *Z* stereochemistry,

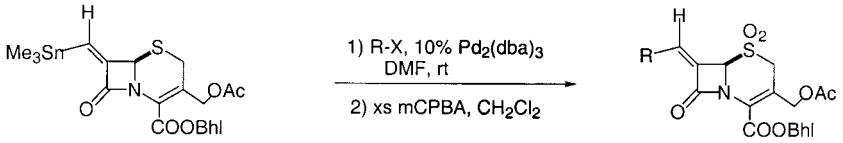


Scheme 2.

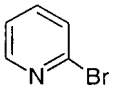
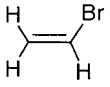
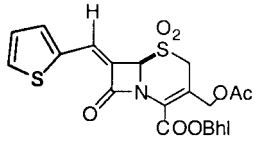
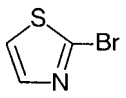
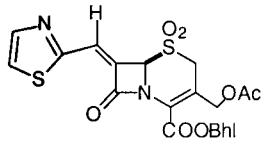
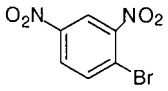
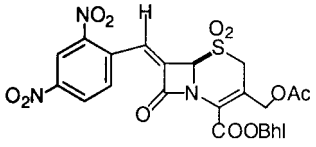


Scheme 3.

Table 2. Stille coupling of **22** with selected organohalides, followed by oxidation

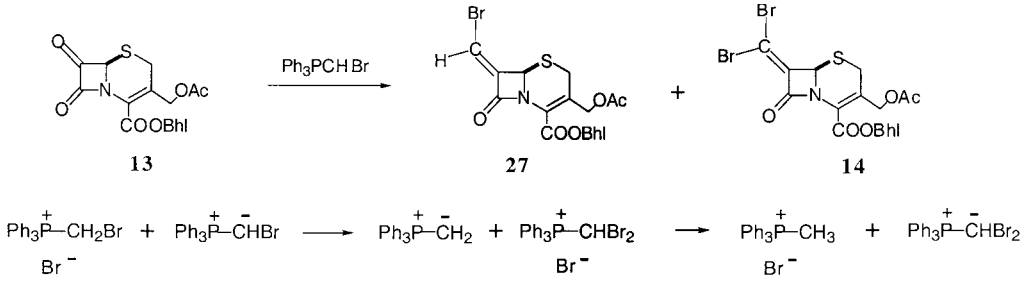


22 **18, 19, 20, 24, 25, 26**

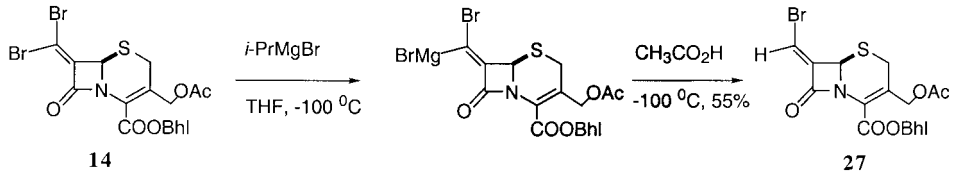
Entry	R–X	Conditions	Product	Yield
1	Ph–I	(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) mCPBA, CH_2Cl_2	**18**	92%
2		(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) mCPBA, CH_2Cl_2	**19**	72%
3		(1) 10% $Pd_2(dba)_3$, DMF, rt, 2 h (2) mCPBA, CH_2Cl_2	**20**	74%
4		(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) mCPBA, CH_2Cl_2	 **24**	87%
5		(1) 10% $Pd_2(dba)_3$, DMF, rt, 10 h (2) mCPBA, CH_2Cl_2	 **25**	68%
6		(1) 10% $Pd_2(dba)_3$, DMF, rt, 2 h (2) mCPBA, CH_2Cl_2	 **26**	74%

we also needed an efficient method for the production of the 7*Z*-bromomethylidene analog **27**. Unfortunately, the most direct route to this compound, involving a Wittig reaction of ketone **13** with (bromomethylidene)triphenylphosphorane, produced an inseparable mixture of monobromide **27** and dibromide **14** (Scheme 4). This unexpected result is likely the result of scrambling of the halides during the production of the ylide as previously observed by Bestman.[28]

Intrigued by the unique selectivity of the reduction of dibromide **14** with metallic zinc, we decided to explore halogen–metal exchange reactions of this compound. When **14** was treated with isopropyl magnesium bromide in THF followed by quenching with mild acid, we were able to selectively obtain the 7*Z*-bromomethylidenecephem **27** (Scheme 5). The origin of this selectivity likely arises from the favorable complexation of the magnesium with the β-lactam carbonyl oxygen.[29] These are the first examples of stable intermediate



Scheme 4.



14 27

Scheme 5.

α-(metallo-alkylidene)-β-lactams. We anticipate that such systems will have substantial synthetic utility, as have the unrelated β-metallo-α,β-unsaturated carbonyl systems in the literature.[30]

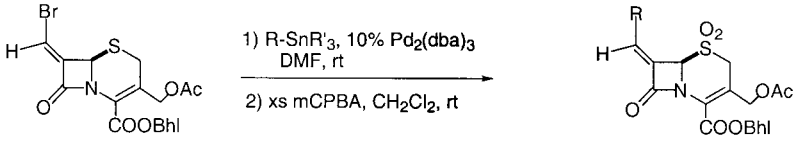
Bromide **27** displayed similar reactivity to that of the 7*E*-bromomethylidenecephem, **15**. As shown below, it was capable of undergoing coupling with a number of different organostannanes to produce the corresponding 7*Z*-methylidenecephems (Table 3).

As before, the vinylstannane **32**, prepared from **27**, could be coupled with a variety of halides, as shown in Table 4.

Dibromide **14** could, itself, be coupled with organostannanes, resulting in a 1:1 mixture of stereoisomers in each case as shown in Table 5.

Treatment of **14** with 2 equivalents of hexamethylditin provided distannane **40** in high yield with little or no isomerization of the double bond, whereas treatment with

Table 3. Stille coupling of **27** with selected organostannanes, followed by oxidation



27 28 to 31

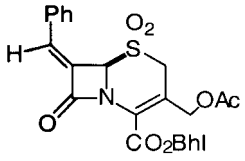
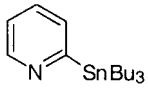
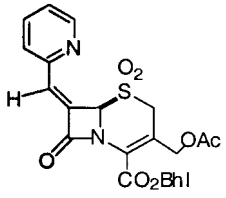
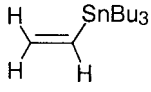
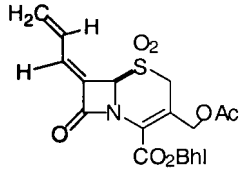
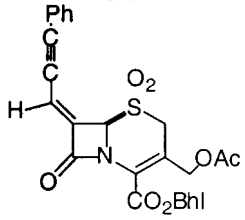
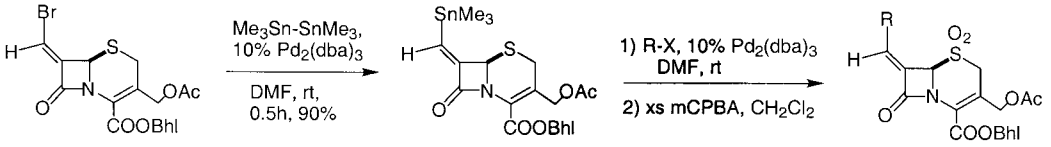
Entry	Stannane	Conditions	Product	Yield
1	Ph–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) xs mCPBA, CH_2Cl_2	 **28**	70%
2		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **29**	59%
3		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **30**	78%
4	Ph–C≡C–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **31**	73%

Table 4. Stille coupling of **32** with selected organohalides, followed by oxidation



27 **32** **28, 29, 33, and 34**

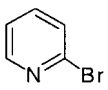
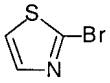
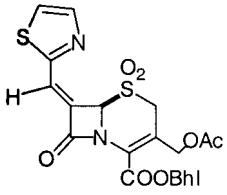
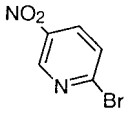
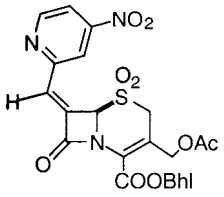
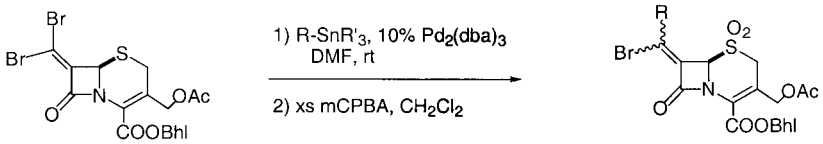
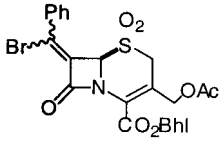
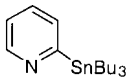
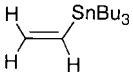
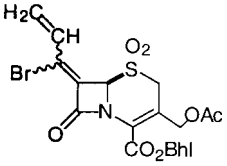
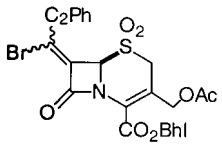
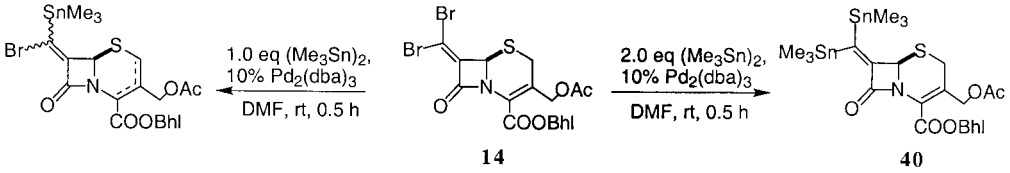
Entry	R–X	Conditions	Product	Yield
1	Ph–I	(1) 10% $Pd_2(dba)_3$, DMF, rt, 6 h (2) xs mCPBA, CH_2Cl_2	**28**	91%
2		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	**29**	67%
3		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **33**	48%
4		(1) 10% $Pd_2(dba)_3$, DMF, rt, 8 h (2) xs mCPBA, CH_2Cl_2	 **34**	82%

Table 5. Stille coupling of **14** with selected organostannanes followed by oxidation



14 **35** through **39**

Entry	Stannane	Conditions	Product	Yield
1	Ph–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 20 h (2) xs mCPBA, CH_2Cl_2	 **35** (*E*) and **36** (*Z*)	46%
2		10% $Pd_2(dba)_3$, DMF, rt to 100°C, 15 h	Decomposition	0%
3		(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **37** (*E*) and **38** (*Z*)	59%
4	Ph–C≡C–$SnMe_3$	(1) 10% $Pd_2(dba)_3$, DMF, rt, 15 h (2) xs mCPBA, CH_2Cl_2	 **39**	54%



14 40

Scheme 6.

1 equivalent of hexamethylditin produced a complex mixture of 7*E* and 7*Z* as well as Δ-2,3 and Δ-3,4 isomers. Distannane **40** refused to couple with organobromides under normal conditions. At higher temperatures, decomposition was observed (Scheme 6).

Experimental

Reagents were purchased from Aldrich and used without further purification. All reactions were conducted under an argon atmosphere. Flash chromatography was carried out on silica gel 60 (230–400 mesh) from EM Science. Melting points were measured in a Mel-Temp II capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX 400 (proton: 400 MHz; and carbon: 100 MHz) using $CDCl_3$ as solvent. Chemical shifts and coupling constants are given in ppm and Hz, respectively. Mass spectrometry was obtained from the Washington University Mass Spectrometry Resource. Spectral data for compounds **13**, **14**, **15**, **18**, **28** and **29** have been previously published.[14]

Benzhydryl 7-oxocephalosporanate (13). To a solution of benzhydryl 7-aminocephalosporonate (0.5 g, 1.15 mmol) in EtOAc (5 mL) were added isopropylnitrite (0.162 g, 1.37 mmol) and trifluoroacetic acid (6.5 mg, 0.05 mmol) and the reaction was stirred for 15 min at rt. The reaction mixture was then concentrated under reduced pressure and redissolved in benzene (5 mL). Propylene oxide (6.7 g, 0.114 mol) was added to this solution followed by rhodium octanoate dimer (2 mg). Evolution of gas was observed immediately after the addition of the catalyst. Stirring was continued for 15 min. Volatiles were removed under reduced pressure to produce the crude ketone (**13**), which was then used without further purification (0.5 g, 90% pure). IR ($CHCl_3$) 3005, 1830, 1790, 1740 cm^{-1}. NMR ($CDCl_3$) δ 7.39–7.20 (11H, m), 7.05 (1H, s), 5.32 (1H, s), 5.07 (1H, d, A of AB q, J=14 Hz), 4.85 (1H, d, B of AB q, J=14 Hz), 3.64 (1H, d, A of AB q, J=18 Hz), 3.44 (1H, d, B of AB q, J=18 Hz), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 188.4 (s), 170.3 (s), 160.1 (s), 158.7 (s), 138.8 (s), 138.6 (s), 128.4, 128.2, 128.1, 127.7, 127.0, 126.9, 126.2, 80.4 (d), 65.8, (d), 62.6 (t), 27.7 (t), 20.5 (q).

General procedure for coupling reactions. A solution of halide (20 mmol), stannane (20 mmol) and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (1 mmol) in anhydrous DMF (3 mL) was stirred under argon at room temperature. After the completion of the reaction (monitored by tlc), DMF was removed under reduced pressure and the residue was partitioned between acetonitrile (10 mL) and pentane (30 mL). The acetonitrile layer was separated, volatiles were removed under reduced pressure and the residue was redissolved in dichloromethane (20 mL). mCPBA (40–60 mmol) was added and the reaction stirred for 30 min at rt. The mixture was then washed, successively, with 20% aqueous $NaHSO_3$, 20% $NaHCO_3$, water, brine and dried (Na_2SO_4). Removal of volatiles under reduced pressure and purification of the residue by column chromatography using 15–30% ethyl acetate in hexane as eluant provided the required products.

Benzhydryl 7-[(*E*)-(2′-pyridyl)methylidene]cephalosporanate 1,1-dioxide (19). Mp 171–174°C; IR ($CHCl_3$) 2965, 2950, 1786, 1350, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.49 (1H, d, J=4.52 Hz), 8.41 (1H, d, J=8.04 Hz), 7.60 (1H, dt, J=1.64, 7.74 Hz), 7.31–7.09 (11H, m), 6.98 (1H, s), 6.82 (1H, s), 5.07 (1H, s), 4.85 (1H, d, A of AB q, J= 14 Hz), 4.50 (1H, d, B of AB q, J=14 Hz), 3.84 (1H, d, A of AB q, J=18 Hz), 3.58 (1H, d, B of AB q, J=18 Hz), 1.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 159.9 (s), 157.3 (s), 151.4 (s), 149.9 (s), 138.0 (s), 136.8 (s), 130.8 (s), 128, 128.5, 128.3, 128.2, 127.6, 127.0, 126.4, 125.7, 124.6, 123.6 (s), 80.4 (d), 69.4 (d), 62.04 (t), 51.3 (t), 20.5 (q). HRMS (FAB) calcd for $C_{29}H_{24}N_2O_7S$ m/z: (MH^+) 545.1382, found: 545.1403.

Benzhydryl 7-[(*E*)-prop-2′-enylidene]cephalosporanate 1,1-dioxide (20). Mp 92–95°C; IR ($CHCl_3$) 3022, 2960, 1785, 1736, 1338, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.25 (10H, m), 7.13–7.09 (1H, m), 6.99 (1H, s), 6.41 (1H, d, J=11.2 Hz), 5.53 (2H, m), 5.44 (1H, m), 4.92 (1H, d, A of AB q, J=14 Hz), 4.67 (1H, d, B of AB q, J=14 Hz), 3.92 (1H, d, A of AB q, J=18 Hz), 3.62 (1H, d, B of AB q, J=18 Hz), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 161.6 (s), 160.1 (s), 139.4 (s), 139.0 (s), 137.2 (s), 130.4, 129.0, 128.5, 128.7, 127.9, 127.6 127.1 126.4 124.2 (s), 81.0 (s), 63.9 (s), 59.7 (d), 51.6 (t), 20.1 (q). HRMS (FAB) calcd for $C_{26}H_{23}NO_7S$ m/z: (MH^+) 494.1273, found: 494.1263.

Benzhydryl 7-[(*E*)-3′-phenylprop-2′-ynlidene]cephalosporanate 1,1-dioxide (21). Mp 97–99°C; IR ($CHCl_3$) 2988, 2110, 1765, 1604, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56–7.24 (15H, m), 6.99 (1H, s), 6.30 (1H, s), 5.19 (1H, s), 5.0 (1H, d, A of AB q, J=14 Hz), 4.69 (1H, d, B of AB q, J=14 Hz), 3.99 (1H, d, A of AB q, J=18 Hz), 3.72 (d, 1H, B of AB q, J=18 Hz), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$) δ170.1 (s), 159.9 (s), 159.1 (s), 151.4 (s), 149.9 (s), 138.0 (s), 136.8 (s), 130.8 (s), 128.2, 127.6, 127.0, 126.4, 126.0, 125.7, 124.6, 123.6, (s), 80.4 (d), 78.2 (s). 71.3 (s), 69.4 (t), 62.04 (d), 51.3 (t), 20.5 (q). HRMS (FAB) calcd for $C_{32}H_{25}NO_7S$ m/z: (MLi^+) 574.1512, found: 574.1517.

Benzhydryl 7-[(*E*)-(trimethylstannyl)methylidene]cephalosporanate (22). IR (neat) 2988, 2920, 1760, 1370, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.25 (10H, m), 7.00 (1H, s), 6.83 (1H, t, J=21.4 Hz), 5.05 (1H, s), 4.90 (1H, d, A

of AB q, J=13 Hz), 4.67 (1H, d, B of AB q, J=13 Hz), 3.50 (1H, d, A of AB q, J=18 Hz), 3.32 (1H, d, B of AB q, J=18 Hz), 1.98 (s, 3H), 0.31 (9H, s) ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 161.0 (s), 160.1 (s), 139.9 (s), 139.3 (s), 138.2 (s), 129.0, 128.5, 128.7, 127.9, 127.6, 127.1, (s), 124.2 (s), 112.1 (d), 80.7 (d), 63.8 (t), 59.5 (d), 27.6 (t), 20.5 (q), -6.3 (q).

Benzhydryl 3-(acetoxymethyl)-7-[(*E*)-(trimethylstannyl)-methylidene]ceph-2-em-4-carboxylate (23) IR (neat) 3002, 1745, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.26 (10H, m), 7.16 (1H, s), 6.89 (1H, s), 6.66 (1H, s), 6.48 (1H, s), 5.19 (1H, s), 4.59 (1H, s), 1.93 (s, 3H), 0.31 (9H, s) ^{13}C NMR ($CDCl_3$) δ 170.0, 162.1, 161.1, 156.6, 139.0, 138.3, 137.8, 129.2, 128.9, 128.7, 127.6, 127.1, 124.8, 124.0, 89.9, 70.2, 60.2, 28.6, 20.8, −6.3.

Benzhydryl 7-[(*E*)-(2′-thiophenyl)methylidene]cephalosporanate 1,1-dioxide (24). Mp 88–91°C; IR ($CHCl_3$) 2988, 2220, 1775, 1604, 1336, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, d, J=6.1 Hz), 7.81 (1H, m), 7.57–7.12 (11H, m), 6.99 (1H, s), 6.77 (1H, s), 5.22 (1H, s), 4.89 (1H, d, A of AB q, J=13 Hz), 4.61 (1H, d, B of AB q, J=13 Hz), 3.81 (1H, d, A of AB q, J=18 Hz), 3.62 (1H, d, B of AB q, J=18 Hz), 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 160.2, 158.3, 151.7, 149.7, 138.2, 136.8, 130.8, 128.0 128.3, 127.6, 127.0, 126.4, 125.7, 124.6, 123.6, 80.4, 69.4, 62.04, 51.3, 20.5.

Benzhydryl 7-[(*E*)-(2′-thiazolyl)methylidene]cephalosporanate 1,1-dioxide (25). Mp 107–110°C; ^{1}H NMR ($CDCl_3$) δ 8.04 (1H, d, J=3.1 Hz), 7.61 (1H, d, J=3.1 Hz), 7.45–7.25 (10H, m), 6.99 (1H, s), 5.14 (1H, s), 4.90 (1H, d, A of AB q, J=14 Hz), 4.67 (1H, d, B of AB q, J=14 Hz), 3.93 (1H, d, A of AB q, J=18 Hz), 3.69 (1H, d, B of AB q, J=18 Hz), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 161.3, 159.8, 151.2, 149.3, 139.4, 137.2, 130.4, 129.0, 128.7, 127.9, 127.6, 127.1, 126.4 124.2, 81.0, 63.9, 59.7, 50.2, 20.1. HRMS (FAB) calcd for $C_{27}H_{22}N_2O_7S_2$ m/z: (MLi^+) 557.1028, found: 557.1024.

Benzhydryl 7-[(*E*)-(2′,4′-dinitrophenyl)methylidene]-cephalosporanate 1,1-dioxide (26). Mp 198–201°C; IR ($CHCl_3$) 3005, 2980, 1774, 1562, 1345, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.95 (1H, d, J=1.68 Hz), 8.50 (1H, d, J=8.4 Hz), 7.92 (1H, d, J=8.4 Hz), 7.41–7.24 (10H, m), 6.93 (1H, s), 5.18 (1H, s), 4.99 (1H, d, A of AB q, J=13 Hz), 4.64 (1H, d, B of AB q, J=13 Hz), 3.93 (1H, d, A of AB q, J=18 Hz), 3.76 (d, 1H, B of AB q, J= 18 Hz), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 161.5, 157.1, 138.8, 137.7, 132.5, 130.1, 129.6, 128.7, 128.4, 128.1, 127.7, 127.3, 127.8, 126.6, 123.9, 123.2, 121.4, 113.4, 99.9, 88.8, 80.1, 70.7, 62.2, 50.9, 21.1.

Benzhydryl 7-[(*Z*)-Bromomethylidene]cephalosporanate (27). A solution of 7-[dibromomethylene]cephalosporanate **14** (0.5 g, 0.84 mmol) in anhydrous THF was cooled to −100°C and a solution of isopropylmagnesium chloride (2.0 M solution in THF, 0.42 mL, 0.84 mmol) was added dropwise over a period of 15 min. After 10 min at −100°C acetic acid (0.1 g, 1.6 mmol) was added via syringe and stirring continued for another 30 min. Saturated NH_4Cl solution was then added and the separated THF layer was dried over Na_2SO_4. Removal of volatiles and purification by column chromatography using 10–20% EtOAc in hexane provided slightly brown solid (0.23 g, 55% yield): mp 72°C; IR ($CHCl_3$) 3065, 2931 1765, 1376, 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.28 (10H, m), 7.20 (1H, s), 6.98 (1H, s), 5.23 (1H, s), 4.97 (1H, d, J=13H), 4.73 (1H, d, J=13H), 3.55 (1H, d, J=18H), 3.34 (1H, d, J=18H), 2.01 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.3, 160.6, 156.0, 144.1, 139.1, 138.9, 128.4, 128.1, 127.7, 127.0, 126.9, 124.3, 110.0, 79.8, 63.0, 57.5, 27.2, 20.5. HRMS (FAB) calcd for $C_{24}H_{20}BrNO_5S$ m/z: (MH^+) 514.0324, found: 514.0328.

Benzhydryl 7-[(*Z*)-prop-2′-enylidene]cephalosporanate 1,1-dioxide (30). Mp 69°C; IR ($CHCl_3$) 3005, 2950, 1788, 1275, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.25 (10H, m), 7.00 (1H, d, J=11 Hz), 6.97 (1H, s), 6.55–6.44 (1H, m), 5.84–5.77 (2H, m), 5.27 (1H, s), 4.99 (1H, d, A of AB q, J=13 Hz), 4.67 (1H, d, B of ABq, J=13 Hz), 3.99 (1H, d, A of AB q, J=18 Hz), 3.76 (d, 1H, B of ABq, J=18 Hz), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 160.8, 157.8, 139.2, 139.0, 137.6, 130.2, 128.2, 127.8, 127.7, 127.4, 127.3, 126.8, 122.9, 122.3, 80.0, 63.1, 58.1, 50.1, 20.6. HRMS (FAB) calcd for $C_{26}H_{23}NO_7S$ m/z: (MLi^+) 500.1355, found: 500.1346.

Benzhydryl 7-[(*Z*)-3′-phenylprop-2′-ynlidene]cephalosporanate 1,1-dioxide (31). Mp 104°C; IR ($CHCl_3$) 2988, 2220, 1775, 1336, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61–7.24 (15H, m), 7.11 (1H, s), 7.00 (1H, s), 5.21 (1H, s), 4.96 (1H, d, A of AB q, J=14 Hz), 4.66 (1H, d, B of AB q, J=14 Hz), 4.00 (1H, d, A of AB q, J=18 Hz), 3.77 (d, 1H, B of AB q, J=18 Hz), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 160.6, 157.1, 138.8, 137.7, 132.5, 130.1, 128.7, 128.4, 128.1, 127.9, 127.7, 127.3, 126.8, 126.6, 123.9, 122.2, 121.4, 114.4, 100.9, 88.8, 80.1, 70.7, 62.2, 50.9, 20.6. HRMS (FAB) calcd for $C_{32}H_{25}N_2O_7S$ m/z: (MLi^+) 574.1512, found: 574.1504.

Benzhydryl 7-[(*Z*)-(trimethylstannyl)methylidene]cephalosporanate (32). (Δ-3,4 isomer): IR (neat) 2996, 2950, 1765, 1325, 1208 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47–7.22 (11H, m), 6.99 (1H, s), 5.11 (1H, s), 4.88 (1H, d, A of AB q, J=14 Hz), 4.69 (1H, d, B of AB q, J=14 Hz), 3.51 (1H, d, A of AB q, J=18 Hz), 3.33 (1H, d, B of AB q, J=18 Hz), 1.99 (s, 3H), 0.31 (9H, s) ^{13}C NMR ($CDCl_3$) δ 170.1, 161.0, 160.1, 141.1, 139.3, 138.2, 129.9, 129.5, 128.7, 127.1, 126.6, 126, 123.2, 109.1, 80.7, 63.8, 60.1, 26.6, 20.9, −6.6.

Benzhydryl 7-[(*Z*)-(2′-thiazolyl)methylidene]cephalosporanate 1,1-dioxide (33). Mp 99–103°C; IR ($CHCl_3$) 3016, 2950, 1764, 1296, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, d, J=3.3 Hz), 7.48–7.25 (11H, m), 6.97 (1H, s), 5.92 (1H, s), 5.05 (1H, d, A of AB q, J=14 Hz), 4.73 (1H, d, B of AB q, J=14 Hz), 4.13 (1H, d, A of AB q, J=18 Hz), 3.76 (1H, d, B of AB q, J=18 Hz), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.0, 159.7, 158.6, 158.4, 145.4, 138.7, 131.2, 128.4, 128.1, 128.0, 127.3, 127.1, 126.9 125.9, 125.7, 123.7, 122.6, 80.2, 72.2, 61.5, 52.4, 20.3. HRMS (FAB) calcd for $C_{27}H_{22}N_2O_7S_2$ m/z: (MLi^+) 557.1028, found: 557.1032.

Benzhydryl 7-[(*Z*)-(5′-nitro-2′-pyridyl)methylidene]cephalosporanate 1,1-dioxide (34). Mp 149–153°C; IR ($CHCl_3$) 3046, 2966, 1786, 1378, 1228 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 9.45 (1H, d, J=2.45 Hz), 8.52 (1H, d, J=8.4 Hz), 7.58 (1H, d, J=8.4 Hz), 7.48–7.25 (11H, m), 6.99 (1H, s), 5.84 (1H, s), 5.17 (1H, d, A of AB q, J=14 Hz), 4.81 (1H, d, B of AB q, J=14 Hz), 4.00 (1H, d, A of AB q, J=17 Hz), 3.78 (d, 1H, B of AB q, J=17 Hz), 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) 170.3, 161.0, 160.2, 151.6 (d), 150.1, 14.6, 139.3, 139.1, 136.6, 128.3, 127.9, 127.6, 127.2, 126.9, 125.8, 123.9, 123.5, 79.4, 63.3, 58.0, 52.3, 20.5.

Benzhydryl 7-*E*-[(1′-Bromo-1′-vinyl)methylidene]cephalosporanate 1,1-dioxide (37). Mp 148–150°C; IR ($CHCl_3$) 3010, 2966, 1764, 1610, 1376 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48–7.24 (10H, m), 6.96 (1H, s), 6.41–6.35 (1H, dd, J=10, 16 Hz), 6.04 (1H, d, J=16.1 Hz), 5.77 (1H, d, J=10.3 Hz), 5.27 (1H, s), 4.93 (1H, d, A of AB q, J=13 Hz), 4.68 (1H, d, B of AB q, J=13 Hz), 3.52 (1H, d, A of AB q, J=18 Hz, 3.35 (d, 1H, B of AB q, J=18 Hz), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 160.8, 157.8, 139.2, 139.0, 137.6, 130.2, 128.2, 127.8, 127.7, 127.4, 127.3, 126.8, 122.9, 122.3, 80.0, 63.1, 58.1, 51.6, 20.6. HRMS (FAB) calcd for $C_{26}H_{22}NO_7BrS$ *m/z*: (MLi^+) 578.0460, found: 578.0437.

Benzhydryl 7-*Z*-[(1′-Bromo-1′-vinyl)methylidene]cephalosporanate 1,1-dioxide (38). Mp 139–143°C; IR ($CHCl_3$) 2995, 2955, 1766, 1625, 1358 cm^{-1}; IR ($CHCl_3$) 2965, 2950, 1786, 1350, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46–7.24 (10H, m), 7.16–7.09 (1H, dd, J=10, 16 Hz), 6.98 (1H, s), 5.90 (1H, d, J=16.1 Hz), 5.64 (1H, d, J=10.3 Hz), 5.24 (1H, s), 4.94 (1H, d, A of AB q, J=13 Hz), 4.70 (1H, d, B of AB q, J=13 Hz), 3.54 (1H, d, A of AB q, J=18 Hz, 3.34 (d, 1H, B of AB q, J=18 Hz), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.9, 161.3, 156.9, 139.7, 139.4, 137.3, 130.9, 128.9, 128.6, 128.4, 128.1, 128.0, 127.8, 127.5, 126.4, 124.2, 80.2, 63.6, 58.7, 51.0, 21.1. HRMS (FAB) calcd for $C_{26}H_{22}NO_7BrS$ *m/z*: (MLi^+) 578.0460, found: 578.0464.

Benzhydryl [3′-phenylprop-2′-ylidene]cephalosporanate 1,1-dioxide (39). Mp 124–126°C; ^{1}H NMR ($CDCl_3$) δ 7.61–7.25 (15H, m), 7.03 (1H, s), 5.41 (1H, s), 4.92 (1H, d, A of AB q, J=13 Hz), 4.70 (1H, d, B of AB q, J=13 Hz), 3.57 (1H, d, A of AB q, J=18 Hz), 3.37 (d, 1H, B of AB q, J=18 Hz), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ ^{13}C NMR ($CDCl_3$) δ 170.3, 160.6, 157.1, 138.8, 137.7, 132.2, 131.1, 128.6, 128.4, 128.2, 127.9, 127.5, 127.1, 126.8, 123.8, 122.8, 121.4, 114.4, 101.2, 89.2, 79.7, 71.6, 51.2, 20.9.

Benzhydryl 7-[bis(trimethylstannyl)methylidene]cephalosporanate (40). IR (neat) 2981, 2914, 1764, 1377, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.43–7.24 (10H, m), 6.99 (1H, s), 4.99 (1H, s), 4.91 (1H, d, A of AB q, J=13 Hz), 4.67 (1H, d, B of AB q, J=13 Hz), 3.50 (1H, d, A of AB q, J=18 Hz), 3.31 (d, 1H, B of AB q, J=18 Hz), 1.97 (s, 3H), 0.31 (9H, t), 0.29 (9H, s). ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 161.2 (s), 160.2 (s), 156.1, 139.3 (s), 128.4(s), 128.3(s), 127.9 (s), 127.8, 127.1, 121.6 (s), 79.4 (s), 63.2 (s), 60.9 (d), 28.2 (t), 20.6 (q), −6.8 (q).

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