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IODINE ATOM TRANSFER ADDITION REACTIONS WITH ALKYNES. PART 2: α-IODOCARBONYLS

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Summary: 1°-Iodo esters, ketones, and nitriles react smoothly in atom transfer addition reactions with alkyl-substituted (nucleophilic) alkynes, but a 3°-iodoester prefers to add to ester-substituted (electrophilic) alkynes. These atom transfer additions are suited for preparing precursors for radical translocation reactions as well for appending β-lactam side chains.

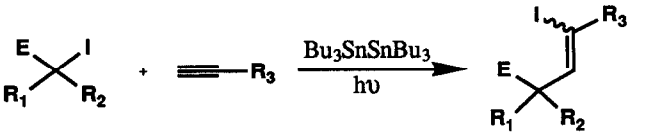
Introduction: The previous paper demonstrated that atom transfer additions of alkyl iodides to electron poor alkynes were potentially useful reactions.[2] However, an expected limitation arose: activating groups were required for the addition step to succeed, but many of these activating groups also stabilized the adduct radicals and reduced the exothermicity of the atom transfer step. This reduction in exothermicity compromised the viability of the reactions. The phenylsulfonyl group was unique in that it could accelerate the radical additions, but it did not stabilize the intermediate radicals. In principle, reversing the electronic requirements in the atom transfer reaction might lead to a more general method. Groups introduced to make a radical more electrophilic (and hence increase its rate of addition to electron rich alkynes) might also stabilize the starting radical relative to the adduct radical (and hence increase the rate of the atom transfer step).

We now present results of a brief study showing that atom transfer additions of α-iodo carbonyls or nitriles to alkynes do indeed have synthetic potential. Further, the results provide some insight into the question of substituent effects on the "philicity" of carbonyl-substituted radicals. The products that form in these additions are ideal precursors for radical translocation reactions. Finally, this method shows promise for generating β-lactams with unusual side chain substituents.

Preparative Studies: Table 1 collects the results of a series of simple preparative experiments. Sunlamp irradiation of a benzene solution (0.5M) of iodoacetonitrile (1 equiv), 1-heptyne (1 equiv), and hexabutylditin (10 mol%) gave vinyl iodide **4a** (E/Z mixture) in 50% isolated yield. The use of excess iodoacetonitrile (2.5 equiv) gave **4a** in about the same yield (48%), but the yield increased to 64% when excess 1-heptyne (2.5 equiv) was used (entry 1). Larger excesses of 1-heptyne were not beneficial, so the standard ratio of iodide to alkyne was set at 1/2.5. Slightly higher yields of adducts **4b** and **4c** formed when the 1-heptyne was reacted with iodoacetone (entry 2, 73%) or ethyl iodoacetate (entry 3, 75%). In each case, there was a modest selectivity in favor of the Z-isomer. In contrast to the successful reactions with 1°-iodo carbonyls, the 3°-iodoester ethyl iodoisobutyrate (**1d**) added to 1-heptyne in very poor yield. Even when 5 equiv of 1-heptyne was used, we isolated **4d** in only 15% yield (entry 4). As in the previous study,[2] the E-vinyl iodide predominated with the 3°-iodide precursor. Since 3°-iodide **1d** is a much better iodine donor than 1°-iodide **1c**, the poor yield in this reaction must be attributed to the radical addition

step. We began to suspect that the radical derived from **1d** was not especially electrophilic, and we wondered if it was even nucleophilic. Indeed, addition of **1d** to methyl propiolate under the standard conditions from the previous paper (excess iodide) gave adduct **5d** in 65% yield (entry 5, 4.4/1, E/Z). In contrast, **1c** showed no tendency to add to methyl propiolate, no matter which reagent was used in excess. Only traces of adduct **5c** formed, and these were not even sufficient to isolate (entry 6).

Table 1. Iodine Atom Transfer Addition of Electron Deficient Iodides to Alkynes.



1a–d **2** $R_3 = C_5H_7$, **3** $R_3 = CO_2Me$ **4** $R_3 = C_5H_7$, $R_3 = CO_2Me$

Entry	Iodide	Akyne	Product	E/Z	Conditions[a]	Yield[b]
1	**1a** E = CN, R_1 = H, R_2 = H	**2** $R_3 = n\text{-}C_5H_{11}$	**4a**	1/2.6	A	64%
2	**1b** E = $COCH_3$, R_1 = H, R_2 = H	**2** $R_3 = n\text{-}C_5H_{11}$	**4b**	1/2.7	A	73%
3	**1c** E = CO_2Et, R_1 = H, R_2 = H	**2** $R_3 = n\text{-}C_5H_{11}$	**4c**	1/2.2	A	75%
4	**1d** E = CO_2Et, R_1 = Me, R_2 = Me	**2** $R_3 = n\text{-}C_5H_{11}$	**4d**	4.5/1	B	15%
5	**1d** E = CO_2Et, R_1 = Me, R_2 = Me	**3** $R_3 = CO_2Me$	**5d**	4.4/1	C	65%
6	**1e** E = CO_2Et, R_1 = H, R_2 = H	**3** $R_3 = CO_2Me$	**5b**	-	A	trace

[a]Sunlamp irradiation; the ratio of alkyne/iodide: A: 2.5/1, B: 5/1, C: 1/2.5.
[b]Yields refer to isolated yields after flash chromatography.

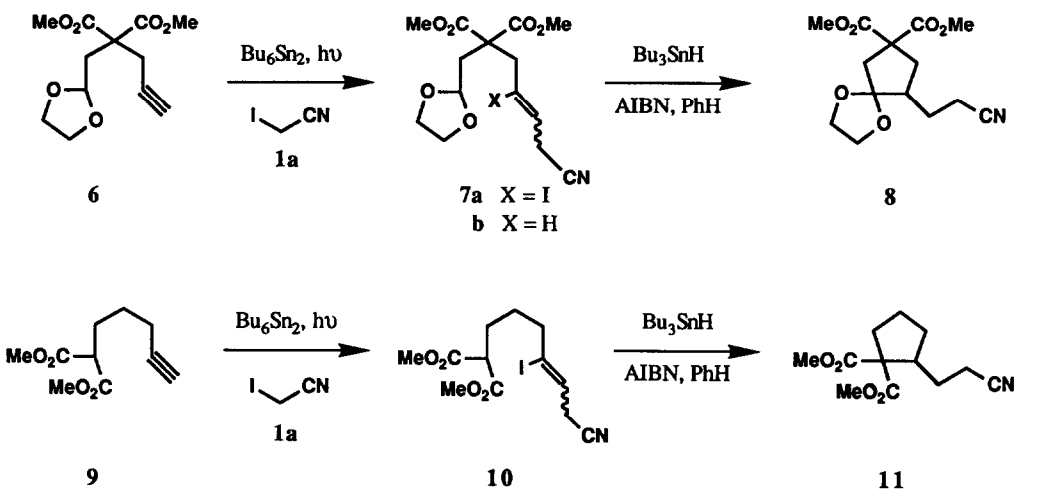
Mechanistic Considerations: These reactions occur by a two step chain of radical addition and atom transfer, as discussed in the previous paper. In contrast to the previous paper, the iodine atom transfer from an α-iodo carbonyl to an unstabilized vinyl radical is highly exothermic. The E/Z ratios shown in Table 1 do not change as a function of time, so we believe that the iodine transfer is irreversible and that the E/Z ratios are kinetically controlled. The trend in selectivity for iodine transfer—larger groups β- to the radical give increasing E-selectivity—is the same as that for hydrogen transfer from tin hydride.[3] This is not surprising since both are atom transfer reactions with small steric requirements and early transition states. Giese has interpreted the trends for hydrogen transfer from tin hydride in terms of a rapidly inverting vinyl radical model.[3] In the previous paper, we have introduced a modified version of the rapidly inverting model.

The contrast in reactivity between the 1°- and 3°-iodo esters is striking. The 1°-iodoester reacts well with an electron rich alkyne but poorly with an electron deficient one (compare entries 3 and 4), while the 3°-iodo ester shows precisely the reverse profile (compare entries 5 and 6). At the outset of our study, carbonyl substituted radicals were generally classed as electrophilic; however, Kharasch observed reactivity differences between 1°- and 3°-ester substituted radicals some 40 years ago.[4] Our results appear to indicate that 1°-ester-substituted radicals are electrophilic but that 3°-ester-substituted radicals are nucleophilic. Further support for this conclusion comes from the work of Hanessian, who introduced a powerful, stereocontroled synthesis of substituted lactones that often relies on cyclizations of ester-

substituted radicals to electron deficient alkenes.[5] We have very recently learned that this conclusion is strongly supported by a quantitative study published in the thesis of W. H. Mehl.[6] Recently, both Fischer[7] and Giese[8] have postulated that a third class exists, ambiphilic radicals, and Fischer has proposed[6] that a 1°-ester substituted radical is ambiphilic. For radicals bearing a single carbonyl group, the border between electrophilic, ambiphilic, and nucleophilic is gray at present. However, for synthetic applications, we can put forth the following recommendation for the time being: if the addition (or cyclization) of a carbonyl-substituted radical fails because the acceptor is not sufficiently reactive, one should consider activating the acceptor not only with electron donating groups, but also with electron withdrawing groups.

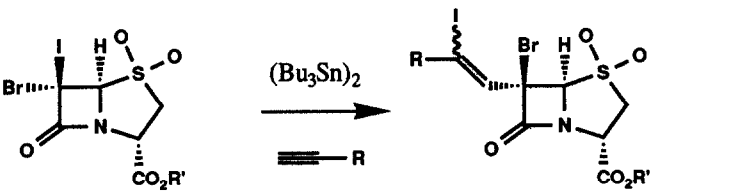
Precursors for Radical Translocation: This atom transfer addition method is ideal for constructing precursors for radical translocation reactions based on the initial formation of vinyl radicals.[9] Scheme 1 shows two examples. (Full details of the radical translocation studies will be reported in a subsequent full paper.) Alkynes **6** and **9** were readily prepared by a standard malonate alkylation sequence (see Experimental). Addition of iodoacetonitrile to **6** under the standard conditions gave **7a** in 55% isolated yield (26/74, E/Z). Syringe pump addition of a benzene solution of tributyltin hydride (0.02M) over 24 h to a refluxing solution of **7a** (0.02M) gave the product **8** resulting from radical translocation and subsequent cyclization in 67% isolated yield.[7] No directly reduced product **7b** was isolated. The rate of syringe pump addition was very important. When the addition was carried out over 1 h under otherwise identical conditions, we isolated **7b** (17%) alongside **8** (40%). The same vinyl radical is generated in the tin hydride reduction of **7a** as in the atom transfer addition of **6** and **1a**; however, when the vinyl radical is generated under the atom transfer conditions, its lifetime is much too short for intramolecular hydrogen transfer because bimolecular iodine transfer from iodoacetonitrile is very fast. However, under the tin hydride conditions, intramolecular 1,5-hydrogen transfer effectively competes with bimolecular hydrogen transfer from tin hydride provided that the tin hydride concentration is kept very low. A similar sequence (**9** → **10** → **11**) was executed in even better yield (step 1, 58%; step 2, 87%) starting from alkyne **9**.

Scheme 1



β-Lactam Side Chains: The preparation of new β-lactams as possible antibiotics or β-lactamase inhibitors is still an important goal in medicinal chemistry. We have briefly investigated the potential of the iodine atom transfer reaction to introduce new β-lactam side chains, and Table 2 contains the results of three experiments.[10] The *S,S*-dioxide of 6α-bromo-6β-iodopenicillanic acid (**12a**) was prepared according to the procedure of Volkmann,[11] and esterified with diphenyldiazomethane to give benzhydrol ester **12b**. Ester **12b** was then reacted with 1-heptyne, trimethylsilylacetylene, and phenylacetylene under a standard set of conditions (2 equiv alkyne, 80°C, 2 h irradiation). Table 2 reports the isolated yields of vinyl iodides that resulted. These yields are only modest (some unchanged starting material was usually present), but the reaction still has some interesting features. As is typical for such β-lactams,[10] a single stereoisomer at the α-position is formed by approach of the alkyne to the less crowded face. Only the iodine atom is abstracted, even though the bromine atom is on the less crowded face. This is because iodides are vastly superior to bromides in typical atom transfer reactions.[12] In addition to the adducts **13** and recovered **12b**, small amounts of a reduced product (iodine replaced by hydrogen) and an inverted product (configuration of iodine and bromine interchanged) typically formed. The structures of these products, taken together with the modest yields, indicate that the addition of the β-lactam radical derived from **12b** to these alkynes is not especially fast. However, useful quantities of iodovinyl-β-lactams are formed, and we believe that these and related compounds will be valuable precursors for making new, biologically active β-lactams.

Table 2. Atom Transfer Additons of β-Lactam **12b**.



12a R' = H
12b R' = $CH(Ph)_2$

13 R' = $CH(Ph)_2$

Entry	Akyne	Product	E/Z	Yield
1	R = C_5H_{11}	**13a**	38/62	20%
2	R = $Si(CH_3)_3$	**13b**	31/69	34%
3	R = Ph	**13c**	25/75	30%

Experimental

2-Iodo-2-methylpropanoic acid, ethyl ester (1d).

A solution of ethyl 2-bromo-2-methylpropionate (1.176 g, 6.029 mmol) and NaI (4.52 g, 30.14 mmol) in acetone (20 mL) was refluxed for 24 h. After addition of water, the product was extracted with diethyl ether (3x). The combined organic phase was washed with water and cold brine, and dried over $MgSO_4$. Concentration gave **1d** (1.043 g, 71%) as a slightly yellow oil: ^1H NMR ($CDCl_3$) δ 4.22 (2H, q, J = 7.1 Hz), 2.07 (6H, s), 1.30 (3H, t, J = 7.1 Hz); IR (thin film) 2978, 2926, 1728, 1462, 1387, 1369, 1275, 1103 cm^{-1}; MS *m/e* 242, 197, 169, 115; HRMS calcd. for $C_6H_{11}IO_2$: 241.9804; found: 241.9803.

(E)- and (Z)-4-Iodonon-3-enenitrile (4a).

By the general procedure in the preceding paper,[2] **4a** was prepared with 1-heptyne (81.6 mg, 0.848 mmol), iodoacetonitrile (56.6 mg, 0.339 mmol), and hexabutylditin (19.7 mg, 0.034 mmol) in benzene (0.7 mL) as a 1/2.6 mixture of E- and Z-isomers. Purification by flash chromatography (hexanes/EtOAc = 10/1) afforded a separable E,Z-mixture of **4a** (57.3 mg, 64%) as a clear oil. The Z-isomer eluted slightly ahead of the E-isomer: ^{1}H NMR ($CDCl_3$) **4aE** δ 6.17 (1H, t, J = 7.2 Hz), 3.08 (2H, d, J = 7.3 Hz), 2.38 (2H, t, J = 7.2 Hz), 1.62-1.15 (6H, m), 0.91 (3H, t, J = 7.2 Hz); **4aZ** δ 5.65 (1H, t, J = 6.5 Hz), 3.20 (2H, d, J = 6.4 Hz), 2.52 (2H, t, J = 7.1 Hz), 1.62-1.15 (6H, m), 0.90 (3H, t, J = 7.2 Hz); IR (thin film, mixture) 2957, 2932, 2858, 2251, 1640, 1466, 1412, 1121 cm^{-1}; MS *m/e*, 263 (M^+), 136 (M^+ – I); HRMS calcd. for $C_9H_{14}IN$: 263.0171; found: 263.0171.

(E)- and (Z)-5-Iodo-4-decen-2-one (4b).

By the general procedure in the preceding paper, **4b** was prepared with 1-heptyne (463.1 mg, 4.815 mmol), iodoacetone (354.4 mg, 1.926 mmol), and hexabutylditin (111.7 mg, 0.193 mmol) in benzene (2.3 mL) as a 1/2.7 mixture of E- and Z-isomers. Purification by flash chromatography (hexanes/EtOAc = 10/1) afforded a separable E,Z-mixture of **4b** (395.3 mg, 73%) as a slightly yellow oil. The Z-isomer eluted slightly ahead of the E-isomer: ^{1}H NMR ($CDCl_3$) **4bE** δ 6.37 (1H, t, J = 7.2 Hz), 3.16 (2H, d, J = 7.3 Hz), 2.35 (2H, t, J = 6.4 Hz), 2.16 (3H, s), 1.55-1.17 (6H, m), 0.90 (3H, t, J = 6.5 Hz); **4bZ** δ 5.80 (1H, t, J = 6.4 Hz), 3.29 (2H, d, J = 6.4 Hz), 2.51 (2H, t, J = 7.1 Hz), 2.18 (3H, s), 1.60-1.20 (6H, m), 0.89 (3H, t, J = 6.7 Hz); IR (thin film, mixture) 2955, 2930, 2857, 1721, 1647, 1458, 1426, 1358, 1252, 1121, 1061 cm^{-1}; MS *m/e* 280 (M^+), 153 (M^+ – I); HRMS calcd. for $C_{10}H_{16}IO$: 279.0246; found: 279.0246.

(E)- and (Z)-4-Iodo-3-nonenoic acid, ethyl ester (4c).

By the general procedure in the preceding paper, **4c** was prepared with 1-heptyne (104.5 mg, 1.087 mmol), ethyl iodoacetate (93 mg, 0.435 mmol), and hexabutylditin (25.2 mg, 0.0434 mmol) in benzene (0.8 mL) as a 1/2.2 mixture of E- and Z-isomers. Purification by flash chromatography (hexanes/EtOAc = 10/1) afforded an inseparable E,Z-mixture of **4c** (101 mg, 75%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$, E,Z-mixture) **4cE** δ 6.35 (1H, t, J = 7.4 Hz), 4.43 (2H, q, J = 7.0 Hz), 3.05 (2H, d, J = 7.4 Hz), 2.37 (2H, t, J = 7.2 Hz), 1.60–1.15 (6H, m), 0.89 (3H, t, J = 6.5 Hz); **4cZ** δ 5.80 (1H, t, J = 6.3 Hz), 4.20 (2H, q, J = 7.1 Hz), 3.17 (2H, d, J = 6.3 Hz), 2.50 (2H, t, J = 7.1 Hz), 1.60-1.15 (6H, m), 0.89 (3H, t, J = 6.5 Hz); IR (thin film, mixture) 2957, 2930, 2859, 1740, 1646, 1466, 1397, 1370, 1254, 1177, 1028 cm^{-1}; MS *m/e* 310, 279, 265, 237, 183; HRMS calcd. for $C_{11}H_{19}IO_2$: 310.0430; found: 310.0430.

(E)- and (Z)-2,2-Dimethyl-4-iodo-3-nonenoic acid, ethyl ester (4d).

By the general procedure in the preceding paper, **4d** was prepared with 1-heptyne (661.5 mg, 6.878 mmol), iodide **1d** (333 mg, 1.376 mmol), and hexabutylditin (79.8 mg, 0.1376 mmol) in benzene (1.6 mL) as a 4.5/1 mixture of E- and Z-isomers. Purification by flash chromatography (hexanes/EtOAc = 20/1) afforded an inseparable E,Z-mixture of **4d** (71.4 mg, 15%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$, E/Z-mixture) **4dE** δ 6.24 (1H, s), 4.12 (2H, q, J = 7.1 Hz), 2.17 (2H, t, J = 7.4 Hz), 1.50-1.40 (2H, m), 1.33 (6H, s), 1.30-1.20 (4H, m), 0.89 (3H, t, J = 6.4 Hz); **4dZ** δ 5.90 (1H, s), 4.21 (2H, q, J = 7.1 Hz), 2.45 (2H, t, J = 7.0 Hz), 1.55-1.40 (2H, m, overlapped with E-isomer), 1.38 (6H, s), 1.35-1.20 (4H, m, overlapped with E-isomer), 0.88 (3H, t, J = 6.4 Hz); IR (thin film, mixture) 2957, 2930, 2870, 1730, 1653, 1466, 1385, 1364, 1113 cm^{-1}; MS *m/e* 338, 265; HRMS calcd. for $C_{10}H_{18}I$ (M^+ – CO_2Et): 265.0453; found: 265.0453.

(E)- and (Z)-2,2-Dimethyl-4-iodo-3-pentenedioic acid, ethyl, methyl esters (5d).

By the general procedure in the preceding paper, **5d** was prepared with methyl propiolate (17.8 mg, 0.212 mmol), iodide **1d** (128 mg, 0.529 mmol), and hexabutylditin (30.7 mg, 0.053 mmol) in benzene (0.4 mL) as a 4.4/1 mixture of E- and Z-isomers. Purification by flash chromatography (hexanes/EtOAc = 10/1) afforded an inseparable E/Z-mixture of **5d** (45.7 mg, 65%) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$, E/Z-mixture) **5dE** δ 6.82 (1H, s), 4.09 (2H, q, J = 7.1 Hz), 3.73 (3H, s), 1.38 (6H, s), 1.23 (3H, t, J = 7.1 Hz); **5dZ** δ 7.60 (1H, s), 4.19 (2H, q, J = 7.1 Hz), 3.84 (3H, s), 1.47 (6H, s), 1.25 (3H, t, J = 7.1 Hz); IR (thin film, mixture) 2979, 2953, 1733, 1471, 1434, 1350, 1227, 1152, 1028 cm^{-1}; MS *m/e* 326, 294, 199; HRMS calcd. for $C_9H_{12}O_3I$ (M^+ – CH_3O): 294.9831; found: 294.9832.

2-(2-Propynyl)propanedioic acid, dimethyl ester.

A solution of dimethyl malonate anion in THF (100 mL) was generated by the addition of dimethyl malonate (7.54 g, 0.057 mol) in THF (50 mL) to a sodium hydride (1.37 g, 0.057 mol) suspension in THF (50 mL) at 0°C. To this was added propargyl bromide (8.15 g, 0.069 mol) dropwise at 25°C. After refluxing for 10 h, the mixture was poured into 1/1 mixture of water and diethyl ether. The aqueous layer was extracted with diethyl ether (3x). The combined organic phase was washed with cold brine (1x) and dried over magnesium sulfate. After concentration, the residue was purified by flash chromatography (hexanes/EtOAc = 5/1) to give the substituted malonate (4.86 g, 50%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 3.76 (6H, s), 3.62 (1H, t, J = 7.2 Hz), 2.80 (2H, 2 H, dd, J = 2.5, 7.2 Hz), 2.30 (1H, t, J = 2.5 Hz); IR (thin film) 3289, 2957, 2124, 1738, 1437 cm^{-1}; MS *m/e* 170, 139, 111, 79, 59.

Carbomethoxy-(2-propynyl)-1,3-dioxolane-2-propanoic acid, methyl ester (6).

To the anion solution from the above malonate in DMF [prepared by the addition of the ester (0.945 g, 5.55 mmol) in DMF (5 mL) to a sodium hydride (134 mg, 5.58 mmol) suspension in DMF (10 mL) at 0°C] was added 2-bromomethyl-1,3-dioxolane (1.113 g, 6.66 mmol) dropwise at 0°C. After stirring at 85°C for 24 h, the mixture was poured into 1/1 mixture of water and diethyl ether. The aqueous layer was extracted with diethyl ether (3x). The combined organic phase was washed with water (3x) and cold brine (1x), and dried over magnesium sulfate. After concentration, the residue was purified by flash chromatography (hexanes/EtOAc = 6/1) to give **6** (626 mg, 44%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 5.01 (1H, t, J = 4.8 Hz), 3.92-3.76 (4H, m), 3.74 (6H, s), 2.98 (2H, d, J = 2.7 Hz), 2.49 (2H, d, J = 4.7 Hz), 2.04 (1H, t, J = 2.7 Hz); IR (thin film) 3283, 2955, 2892, 2782, 2120, 1740, 1437, 1364, 1291, 1138, 1099, 1030 cm^{-1}; MS *m/e* 256, 225, 215, 197, 170.

(E)- and (Z)-2-Carbomethoxy-2-(4-cyano-2-iodo-2-butenyl)-1,3-dioxolane-2-propanoic acid, methyl ester (7).

To a benzene (5 mL) solution of **6** (1.311 g, 5.12 mmol) was added iodoacetonitrile (426.9 mg, 2.56 mmol) and hexabutylditin (148.3 mg, 0.26 mmol). After the mixture was stirred at 25°C in the dark for 1 min, it was transfered to a flat Pyrex flask. The solution was irradiated with a sunlamp at 80-85°C for 1 h. After concentration, the crude product was purified by flash chromatography (hexanes/EtOAc = 3/1) to give the vinyl iodide **7** (595.2 mg, 55%) as an inseparable 1/2.9 mixture of E- and Z-isomers: ^{1}H NMR ($CDCl_3$) **7E** δ 6.42 (1H, t, J = 7.2 Hz), 4.94 (1H, t, J = 4.2 Hz, overlapped with Z-isomer), 4.0-3.75 (4H, m, overlapped with Z-isomer) 3.75 (6H, s), 3.30 (2H, s), 3.27 (2H, d, J = 7.4 Hz), 2.43 (2H, d, J = 4.5 Hz); **7Z** δ 5.98 (1H, t, J = 6.4 Hz), 4.97 (1H, t, J = 4.5 Hz), 4.0-3.75 (4H, m, overlapped with E-isomer) 3.75 (6H, s), 3.45 (2H, s), 3.19 (2H, d, J = 6.6 Hz), 2.36 (2H, d, J = 4.3 Hz); IR (thin film, mixture) 2954, 2893, 2252, 1733, 1653, 1436, 1206 cm^{-1}; MS *m/e* 422, 392, 364, 296; HRMS calcd. for $C_{13}H_{15}NO_5I$ ($M^+ - CH_3O$): 391.9995, found: 391.9996.

9-(2-Cyanoethyl)-1,4-dioxaspiro[4,4]nonane-7,7-dicarboxylic acid dimethyl ester (8).

To a solution of **7** (214.5 mg, 0.51 mmol) in refluxing benzene (25 mL) was added a solution of tributyltin hydride (177.0 mg, 0.61 mmol) and AIBN (4.2 mg, 0.026 mmol) in benzene (25 mL) via syringe pump over 24 h. After concentration, the residue was dissolved in ether (5 mL). The excess Bu_3SnH was destroyed by the addition of a ether solution of iodine (30 mg, 0.12 mmol). After the addition of DBU (186 mg, 1.22 mmol) to the ether solution, the mixture was stirred at 25°C for 30 min. The white precipitate was filtered off and the filtrate was concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc = 2/1) to give the cyclic ketal **8** (101 mg, 67%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 3.95-3.87 (4H, m), 3.74 (3H, s), 2.60-2.51 (2H, m), 2.41-2.24 (4H, m), 2.06-1.65 (3H, m); ^{13}C NMR ($CDCl_3$) δ 172.2 (s), 171.7 (s), 119.7 (s), 115.6 (s), 64.9 (t), 64.4 (t), 55.6 (s), 53.1 (q), 53.0 (q), 43.9 (d), 42.6 (t), 36.4 (t), 24.2 (t), 15.6 (t); IR (thin film) 2955, 2893, 2246, 1739, 1733, 1435, 1269, 1162, 1055 cm^{-1}; MS *m/e* 297, 266, 257, 184; HRMS calcd. for $C_{14}H_{19}NO_6$: 297.1212; found: 297.1211.

(4-Pentynyl)-propanedioic acid, dimethyl ester (9).

To a suspension of sodium hydride (3.4 g, 0.142 mol) in DMF (30 mL) was added a solution of dimethyl malonate in DMF (30 mL) dropwise at 0°C. The mixture was stirred at 25°C for 1 h. To the anion solution was added 5-iodo-1-pentyne (5.488 g, 28.3 mmol) dropwise at 0°C. After the mixture was stirred at 60°C for 12 h, it was poured into 1/1 mixture of water and diethyl ether. The aqueous layer was extracted with diethyl ether (3x). The combined organic phase was washed with water (1x) and cold brine (1x), and dried over magnesium sulfate. After concentration, the residue was purified by flash chromatography (hexanes/EtOAc = 10/1) to give **9** (2.451 g, 51%) as a clear oil. ^{1}H NMR

($CDCl_3$) δ 3.75 (6H, s), 3.40 (1H, t, J = 7.2 Hz), 2.21 (2H, dt, J = 2.7, 6.7 Hz), 2.10–1.95 (3H, m), 1.50–1.65 (2H, m); IR (thin film) 3291, 2957, 2872, 2118, 1734, 1437, 1345, 1154 cm^{-1}.

(E)- and (Z)-(4-Iodo-6-cyano-4-hexenyl)propanedioic acid, dimethyl ester (10).

To a benzene (2.6 mL) solution of **9** (442 mg, 2.23 mmol) was added iodoacetonitrile (217 mg, 1.30 mmol) and hexabutylditin (73 mg, 0.13 mmol). After the mixture was stirred at 25°C in the dark for 1 min, it was transfered to a flat pyrex flask. The solution was irradiated with a sunlamp at 80-85°C for 1 h. After concentration, the crude product was purified by flash chromatography (hexanes/EtOAc = 4/1) to give the vinyl iodide **10** (277.7 mg, 58%) as an inseparable 1/2.5 mixture of E- and Z-isomers: ^1H NMR ($CDCl_3$) **10E** δ 6.20 (1H, t, J = 7.3 Hz), 3.75 (3H, s, overlapped with Z-isomer), 3.38 (1H, t, overlapped with Z-isomer) 3.09 (2H, d, J = 7.3 Hz), 2.43 (2H, t, J = 7.3 Hz), 1.95-1.50 (4H, m); **10Z** δ 5.70 (1H, t, J = 6.4 Hz), 3.75 (3H, s), 3.39 (1H, t, J = 7.4 Hz) 3.20 (2H, d, J = 6.5 Hz), 2.55 (2H, t, J = 7.3 Hz), 1.95-1.50 (4H, m); IR (thin film) 2953, 2865, 2251, 1732, 1642, 1435, 1345, 1217, 1151 cm^{-1}; MS *m/e* 365, 334, 302, 238; HRMS calcd. for $C_{12}H_{16}INO_4$: 365.0124, found: 365.0194.

2-(2-Cyanoethyl)-1,1-cyclopentanedicarboxylic acid, dimethyl ester (11).

To a solution of **10** (339.9 mg, 1.01 mmol) in refluxing benzene (50 mL) was added a solution of tributyltin hydride (352.1 mg, 1.21 mmol) and AIBN (8.2 mg, 0.05 mmol) in benzene (25 mL) via syringe pump over 24 h. After concentration, the residue was dissolved in ether (5 mL). The excess Bu_3SnH was destroyed by the addition of a ether solution of iodine (60 mg, 0.24 mmol). After the addition of DBU (372 mg, 2.44 mmol) to the ether solution, the mixture was stirred at 25°C for 30 min. The white precipitate was filtered off and the filtrate was concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc = 4/1) to give the cyclic compound **11** (182.2 mg, 87%) as a clear oil: ^1H NMR ($CDCl_3$) δ 3.74 (3H, s), 3.72 (3H, s), 2.60~2.30 (4H, m), 2.10-1.35 (7H, m); ^{13}C NMR ($CDCl_3$) δ 172.5 (s), 171.5 (s), 119.6 (s), 63.1 (s), 52.6 (q), 52.3 (q), 45.8 (d), 34.7 (t), 30.6 (t), 27.4 (t), 22.7 (t), 16.4 (t); IR (thin film) 2955, 2874, 2245, 1728, 1435, 1269, 1203, 1156, cm^{-1}; MS *m/e* 239, 208, 145; HRMS calcd. for $C_{12}H_{17}NO_4$: 239.1158, found: 239.1156.

Benzhydryl 6α-Bromo-6β-iodopenicillanate *S,S*-dioxide (12b).

The free acid **12a** was prepared according to Volkmann.[11] Esterification in ethyl acetate with diphenyl diazomethane cleanly produced **12b** in 80-90% yields. The stereochemical assignment at the 6-position of this compound is based on x-ray crystallographic data of pivaloyl 6α-bromo-6β-iodopenicillanate:[13] mp 140° (dec.); ^1H NMR ($CDCl_3$) δ 7.36 (m, 10H), 6.96 (s, 1H), 4.93 (s, 1H), 4.54 (s, 1H), 1.59 (s, 3H, CH_3), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.66, 164.61, 138.53, 138.31, 128.70 (2C), 128.61 (2C), 128.34 (2C), 127.4 (2C), 126.69 (2C), 79.36, 72.1, 64.41, 62.07, 19.06, 18.64; Opt. Rotation ($CHCl_3$) $[\alpha]_D^{25}$ = +171 ± 1; IR (KBr) cm^{-1}: 3088, 3064, 3032, 2982, 2937, 1805, 1744; MS (DCI-Ammonia) (*m/e*): 623, 621 ($M^+ + NH_4^+$); Anal. calcd. for $C_{21}H_{19}BrINO_5S$: C, 41.74; H, 3.17; N, 2.32; Br, 13.22; I, 21.00. Found: 41.42; H, 3.10; N, 2.23; Br, 13.11; I, 20.84.

General Procedure for Reaction of Benzhydryl 6α-Bromo-6β-iodopenicillanate *S,S*-dioxide with Terminal Acetylenes.

To a 0.35M benzene solution containing the benzyhydryl 6,6-bromoiodopenicillanate *S,S*-dioxide (604 mg, 1 mmol, 3.5 m benzene) was added Me_6Sn_2 (33 mg, 0.1 mmol) and the acetylene (2.2 mmol). The solution was degassed with argon and then irradiated (300W lamp) for 2 h under reflux. The crude reaction mixtures were absorbed directly onto silica gel, then purified by flash silica gel column chromatography (EtOAc - hexane gradient elutions). The 6α-iodovinylsubstituted products isolated were **E** and **Z** geometric isomers (preparatively inseparable), usually mixed with small amounts of unreacted penicillanate and/or reduced penicillanate (again, preparatively inseparable). From the ^1H NMR spectrum of each product mixture an adjusted yield was calculated.

Benzhydryl 6β-Bromo-6α-[1-(E & Z-2-iodoheptenyl)] penicillanate *S,S*-dioxide (13a).

^1H NMR ($CDCl_3$) - E/Z ratio is 1.6:1; δ 7.36 (m, 10H), 6.96 (s, 1H, benzhydryl methine), 6.33 and 6.62 (vinylic H's of **Z** and **E** isomers respectively), 5.08, 4.59, 4.57, 4.55 (4 singlets of isomeric H_3 and H_5), 2.6 (m, 2H, allylic CH_2), 1.61, 1.59 (2 singlets, 3H, CH_3 + H_2O impurity), 1.4 (3H, m), 1.3 (m, 6H, $3CH_2$),1.26, 1.12 (2 singlets, 3H, CH_3); IR (KBr) cm^{-1}: 3089, 3064, 3032, 2957, 2932, 1808, 1756, 1610; MS (DCI-Ammonia) *m/e*: 719, 717 ($M^+ + NH_4^+$).

6β-Bromo-6α-[1-(E & Z-2,2-iodotrimethysilylethenyl)] penicillanate *S,S*-dioxide (13b).
^{1}H NMR ($CDCl_3$): E/Z ratio is 0.45; δ 7.4 (m, 10H, aromatic), 6.95 (benzhydryl methine), 7.6 and 6.86 (2 singlets, vinyl H, ratio = 1.96 respectively); 5.1, 4.69 (2 singlets, H_3, ratio 0.45), 4.61, 4.59 (2 singlets, H_3, ratio = 0.42), 1.62, 1.59 (2 singlets, 3H, CH_3 ratio = 0.5), 1.12, 1.11 (2 singlets, 3H, CH_3, ratio = 0.5 respectively), 0.41, 0.23 (2 singlets, 9H, $Si(CH_3)_3$ ratio 2 : 1 respectively). IR (KBr) cm^{-1}: 3088, 3063, 3033, 2958, 2900, 1809, 1754; MS (DCI-Ammonia) m/e: 721,719 (M+ NH_4^+).

Benzhydryl 6β-Bromo-6α-[1-(E & Z-2,2-iodophenylethenyl)] penicillanate *S,S*-dioxide.
The yield of product mixture from the column was 522 mg contaminated with approximately 2% EtOAc (9 mg) and roughly 50% (302 mg) starting material and a little epimerized starting material. In a scale-up experiment, 3.36 g (5.6 mmol) starting material was reacted with phenylacetylene (14 mmol, 1.43g). The Z-isomer 1.2 g (30%) was obtained pure by fractional crystallization (toluene/hexane), m.p. 135°C(dec.). ^{1}H NMR ($CDCl_3$) δ 6.89 (s, benzhydryl methine), 6.83 (s, vinyl H), 4.46 (s, H_5), 3.95 (s, H_3) 1.48 (s, 3H, CH_3), 0.82 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.80, 165.03, 140.14, 138.62, 138.33, 132.91, 130.0-126.75 (15 aromatic C's), 104.1, 79.45, 67.82, 64.33, 63.1, 57.32, 19.49, 18.90; IR (KBr) cm^{-1}: 3064, 3037, 2999, 1815, 1757; Opt. Rotation ($CHCl_3$) $[\alpha]_D^{26}$ = + 231° ± 1; Anal. calcd for $C_{29}H_{25}BrINO_5S$: C, 49.31; H, 3.57; N, 1.98; S, 4.54, Br, 11.31, I, 17.97. Found: C, 49.66; H, 3.55; N, 1.77; S, 4.61; Br, 11.80; I, 17.30.

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