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STEREOSELECTIVE CONSTRUCTION AND SYNTHETIC APPLICATIONS OF PHENYLTHIO SUBSTITUTED IODOOLEFINS

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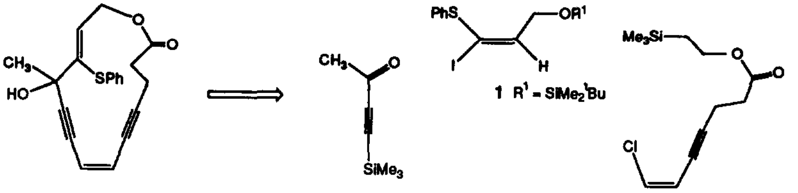
Summary: (E)- and (Z)-Phenylthio substituted iodoolefins 1 and 2 have been synthesized stereoselectively via lower order stannylcuprate addition to and hydroalumination of appropriate alkyne precursors. Their utility in model studies on the synthesis of calichemicin/esperamicin and neocarzinostatin aglycones is shown.

In connection with ongoing studies on the implementation of a unified Claisen rearrangement strategy for the synthesis of calichemicin/esperamicin[2] and neocarzinostatin[3] aglycones, (E)- and (Z)-phenylthio substituted iodoolefins 1 and 2 were required for effecting the overall transformations depicted in eq 1 and eq 2 respectively. At the outset, the importance of both vinyl sulfides[4] and vinyl iodides[5] in organic synthesis rendered the previously unknown olefins 1 and 2 particularly attractive targets.



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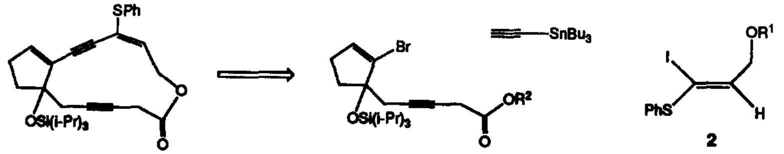
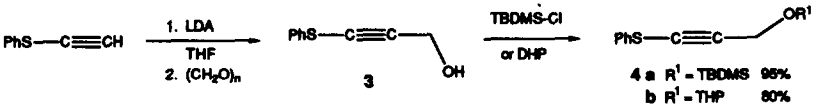


(2)

It was thought that phenylthiopropargylic alcohol 3 or its corresponding ethers 4 could serve nicely as precursors to the requisite vinyl sulfides 1 and 2 (vide infra). Consequently, 3 was prepared by hydroxymethylation of phenylthioacetylene with solid paraformaldehyde in 84% isolated yield (eq 3). In turn, the synthesis of phenylthioacetylene[6] was accomplished in two steps and 75% overall yield from phenyl vinyl sulfide,[7] as described in eq 4. Protection of alcohol 3 with either tert-butyldimethylsilyl (TBDMS)



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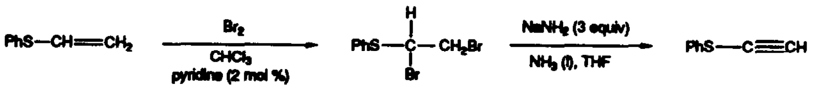


(4)

chloride or dihydropyran (DHP) furnished the desired propargylic ethers 4 (eq 3). Alternatively, alkynes 4 have been prepared in 85% yield (purified by SG flash-column chromatography) by sequential treatment of the TBDMS or THP ethers of propargyl alcohol with lithium diisopropylamide (LDA; THF, -78→20°C, 15 min) and phenyl phenylthiosulfonate[8] (THF, -78→23°C).

After considerable experimentation[9] it was discovered that treatment of phenylthioalkyne 4a with the lower order tributylstannylcuprate (2 equiv), prepared by transmetallation of tributylstannyllithium (Bu_3SnH; LDA, THF, -78→-30°C) with the soluble copper salt $CuCN \cdot 2LiCl$ (THF, -50°C),[10] gave rise to (E)-tributylstannylalkene 5 in 65% isolated yield (preparative SG-TLC; 0.5 mm thickness; 15% benzene, 85% hexane).[11]

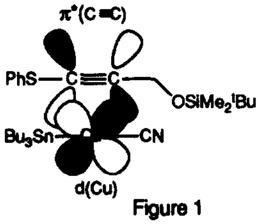
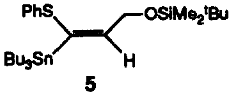


Figure 1



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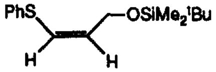

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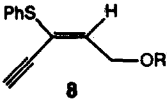

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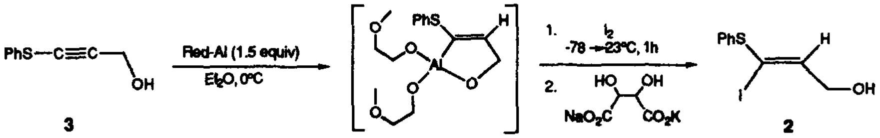
The regioselectivity of this addition was found to be complete[12] and the (E):(Z) ratio (stereoselectivity) within regioisomer 5 has been estimated to be at least 10:1 (by 270 MHz ^1H NMR integration).[13] Regiochemical and stereochemical assignments of structure 5 were made based on the vinylic hydrogen (t, 6.12 ppm) coupling constants (^1H NMR) of 5.1 Hz (allylic hydrogens) and 48.5 Hz (average value, cis Sn^{117}/Sn^{119}) respectively.[14]

A small amount of (Z)-phenylthioalkene 6 was also detected (SG-TLC; 1% Et_3N/10% benzene, 90% hexane) and subsequently isolated (15% yield), suggesting the in situ generation of a Cu(I) hydride species.[15] Accordingly, the yield of 6 could be minimized (<5%) by using tributylstannyllithium prepared from hexabutyldistannane and n-butyllithium[16] under aprotic conditions.[17] Conversion of 5 to the desired (E)-vinyl iodide 1 was accomplished by iododestannylation (1 equiv of I_2; CH_2Cl_2, 0→23°C; quantitative yield) which proceeded without concomitant oxidation of sulfur.

One possible explanation for the observed stereoselectivity and regioselectivity[12] may involve an unsymmetrical bidentate interaction of a d(Cu) orbital with one of the two π^* molecular orbitals of the triple bond as has been proposed by Corey and Boaz (Figure 1).[18] Regarding this unsymmetrical interaction, Marino has suggested that a cyano ligand increases the Lewis acidity of the copper atom in the cuprate,[19] thereby favoring its complexation with the electron-rich alkyne 4a in this case[12] and enhancing the polarization of the triple bond (the carbon α to sulfur is thought to be relatively electron deficient). Experimental evidence in support of this rationale is being pursued.

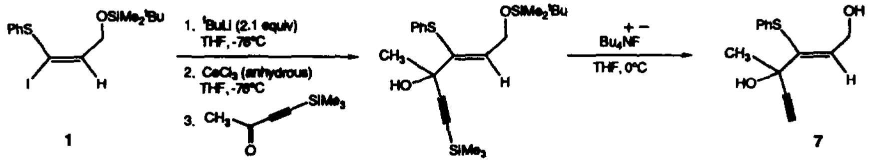
On the other hand, the synthesis of (Z)-phenylthio substituted iodoolefin 2 (R^1=H) was achieved by a modification of the Corey reductive halogenation ($LiAlH_4$, $NaOCH_3$; I_2) of ethynyl carbinols.[20] Thus, reaction of 3 with bis(2-methoxyethoxy)aluminum hydride (Red-Al) followed by aluminum-iodine exchange and standard aqueous workup,[21] provided stereodefined (Z)-allylic alcohol 2 (R^1=H) in 80% isolated yield (eq 5).22 Treatment of



(5)

alcohol $\underline{2}$ with TBDMS chloride (Et_3N, cat. DMAP; CH_2Cl_2, 0°C) or DHP (neat; cat. PPTS, 0→23°C) resulted in the corresponding ethers $\underline{2}$ (R^1 = TBDMS, 90%; R^1 = THP, 85%).

Transmetallation of iodovinyl ether $\underline{1}$ with tert-butyllithium and transfer of the resultant vinyllithium compound to a suspension of ceric chloride in tetrahydrofuran (THF) provided a nucleophilic vinylcerium reagent.[23] Addition of this organocerium(III) reagent to 4-trimethylsilyl-3-butyn-2-one[24] resulted in the expected tertiary and propargylic alcohol (eq 6) which upon desilylation gave rise to diol $\underline{7}$ (50% overall yield, 85% based



(6)

on recovered (Z)-olefin $\underline{6}$). Enyne diol $\underline{7}$ represents an important intermediate for the synthesis of the enediyne lactone shown in eq 1.

In conclusion, palladium-catalyzed coupling[25] of (Z)-iodosilyl ether $\underline{2}$ (R^1 = TBDMS or THP) with ethynyltributylstannane furnished a good yield (85%) of enyne $\underline{8}$ which is a valuable precursor to the neocarzinostatin aglycone model lactone shown in eq 2. Work is in progress on the synthesis of the calichemicin/esperamicin model lactone (eq 1) from alcohol $\underline{7}$ and chloroenyne ester[26] (eq 1) as well as other applications of these useful iodoolefins.

Acknowledgement

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