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A Cycloaddition Strategy Directed Toward the Spiro Ring System of the Ginkgolides

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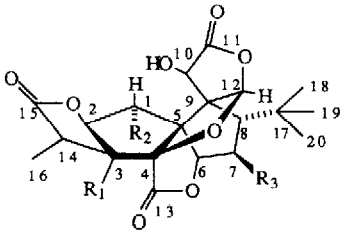
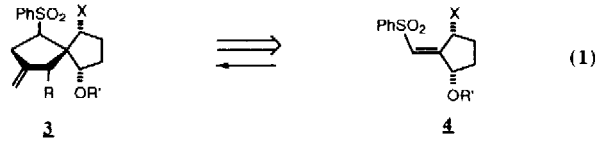
Summary. A diastereocontrolled [3+2] cycloaddition to a sterically congested γ-alkoxy-β,β-disubstituted-α,β-unsaturated sulfone combined with a thiomethylenation of an enol silyl ether provides the core spirocarbocyclic rings of the ginkgolides.

Although the structural elucidation of the ginkgolides was reported two decades ago, these challenging structures did not attract attention of synthetic chemists.[1] Recent revelations regarding the antagonist properties of ginkgolide B (1) toward the platelet activating factor and the insect antifeedant properties of ginkgolide A (2) stimulate interest in these architecturally beautiful molecules.[3] In developing a synthetic strategy, we envisioned a cycloaddition approach[4] to the core spirocarbocycle 3a and 3b as outlined in eq 1. To explore this strategy, the feasibility of such a hindered acceptor to



	R_1	R_2	R_3	
Ginkgolide A	OH	H	H	2
B	OH	OH	H	1
C	OH	OH	OH	
D	H	OH	OH	



3
a) R=H, R'=TBDMS, X=H
b) R=H, R'=TBDMS, X=OTBDMS

4
a) R'=TBDMS, X=H
b) R'=TBDMS, X=OTBDMS

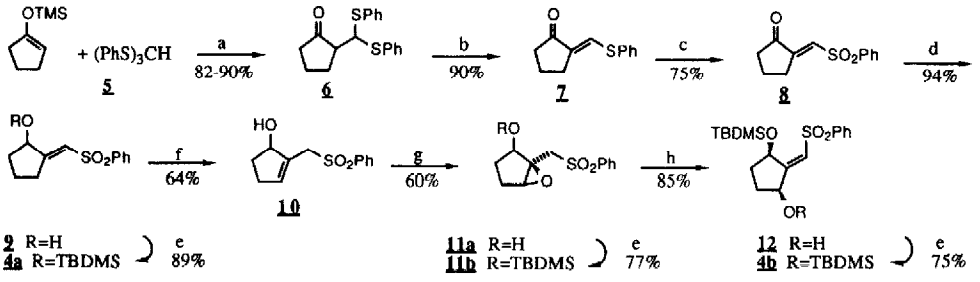
(1)

participate in the metal catalyzed reaction must be established. If successful, the stereochemical consequences of the alkoxy group on the reaction would be of great interest.

Scheme 1 outlines the synthesis of the two acceptors. To create a thiomethylenation, we utilized thionium ion chemistry.[5,6,7] Condensation of the orthothiester 5 with the enol silyl ether of cyclopentanone in the presence of stannic chloride provides the desired thioacetal 6[8] which smoothly eliminates with DBU to give the elimination product as a single geometric isomer. The oxidation to the sulfone proved surprisingly sensitive to experimental conditions. Controlling the pH at 5.5-6.0 with a borate buffer and minimizing

reaction and work-up time to avoid over-oxidation with oxone[9] gave the ketosulfone 8[8] as a crystalline solid, mp 61-62°. Reduction with sodium borohydride required the presence of

Scheme 1. Synthesis of Cycloaddition Acceptors



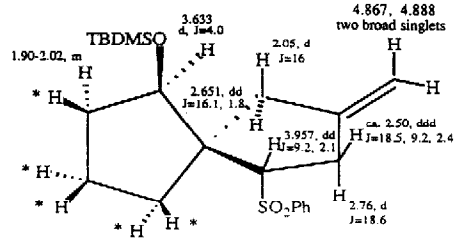
a) $SnCl_4$, CH_2Cl_2, -45°. b) DBU, CH_2Cl_2, 0°. c) Oxone, borate buffer, CH_3OH, H_2O, rt. d) $NaBH_4$, $CeCl_3$, CH_3OH, rt. e) TBDMS-Cl, $C_3H_4N_2$, DMAP, DMF, rt. f) KOC_4H_9-t, t-C_4H_9OH, rt. g) $VO(acac)_2$, t-C_4H_9OOH, CH_2Cl_2, rt. h) LDA, ether, 0°.

ceric chloride to avoid conjugate reduction.[10] Standard silylation produces our first substrate 4a.[8]

The second substrate requires diastereoselective introduction of an allylic oxygen. To utilize the base catalyzed opening of a β, γ-epoxysulfone, we require isomerization of the exocyclic double bond of 4a, 8, or 9 to the thermodynamically more stable endocyclic position. The high base instability of enone 8 led to modest yields of the desired rearranged product upon treatment with 2 eq of DBU in methylene chloride. A more satisfactory result was obtained by subjecting allylic alcohol 9 to base. Hydroxyl directed epoxidation, silylation, base catalyzed elimination and final silylation then provides the silyl ether 4b of the diol 12 as our second acceptor.

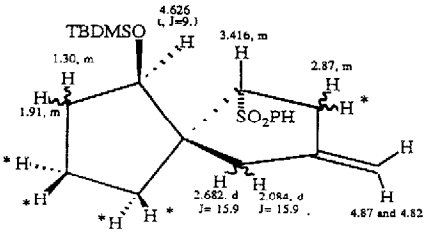
Cycloaddition of 4a (0.4M) with 2-acetoxymethyl-3-trimethylsilyl-1-propene catalyzed by a Pd(0) complex generated from 10 mol% palladium acetate, 60 mol% triisopropylphosphite, and 20 mol% n-butyllithium in toluene at 115-120° for 30h gave a 67% yield of a 4.2:1 diastereomeric mixture of cycloadducts[8] depicted in Fig. 1. The observations of positive

Fig 1. ^{1}H-NMR Data for Cycloadducts 3a



MAJOR

*: not assigned multiplets at 1.48-1.60(2H), 1.75-1.88(2H), 2.16-2.25(1H).
aromatic signals at 7.92-7.84(2H), 7.65-7.50(3H).

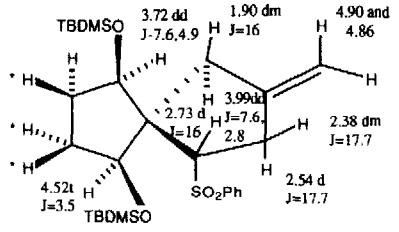


MINOR

*: not assigned multiplets at 2.40-2.28(2H), 1.76-1.62(3H).
aromatic signals at 7.92-7.83(2H), 7.67-7.50(3H).

NOE's between the proton resonating at δ 3.633 and δ 2.05 in the major adduct and δ 4.626 and δ 3.416 in the minor adduct allow assignment of stereochemistry as depicted. Similar cycloaddition with the disiloxy acceptor 4b gave a single stereoisomeric adduct[8] in 76% yield. Fig 2 summarizes the ^{1}H nmr data. Based upon analogy to the above major cycloadduct, the stereochemistry depicted in Fig 2 is assigned.

Fig 2. ^{1}H-NMR Data for Cycloadduct 3b



*: not assigned multiplets at 2.17-2.02(3H), 1.97(1H).
aromatic signals at 7.92-7.84(2H), 7.62-7.47(3H).

The facility of the cycloadditions with the parent trimethylenemethane system led us to also examine simultaneous introduction of a carboxyl group. Unfortunately, all attempts to perform a carboxylative cycloaddition failed.[11] The lower reactivity associated with a carboxylated -trimethylenemethane palladium complex and, equally important, the increased steric hindrance of the anionic pole of the zwitterionic intermediate conspire to prevent attack on our very hindered acceptors.

The similarity of our [3+2] cycloaddition to the Diels-Alder reaction tempts us to explain our results using similar arguments. Indeed, in several previous cases, close analogy does exist.[12] Thus, while electrostatic interactions, orbital interactions, van der Waals-London attractions, etc., have been invoked to explain the effect of an allylic oxygen on diastereofacial selectivity, simple steric effects do account for the observations herein. The fact that the diastereomeric ratio increases from 4.2:1 to >100:1 in going from the monosiloxy acceptor 4a to the disiloxy acceptor 4b supports this notion.

The success of our cycloaddition and the excellent diastereofacial selectivity achievable leads us to explore this strategy towards the ginkgolides. In contrast to this success, Diels-Alder reactions with such substrates normally fail. Consideration of the range of possibilities for acceptors in this metal catalyzed cycloaddition is considerably broadened by the success reported herein. It should be noted that the use of the triisopropylphosphite palladium(0) catalyst appears to be the most general for the cycloadditions. Nevertheless, while it has become our first choice of catalyst in general, we do have some examples where other ligands are mandatory.

A second aspect of this synthesis relates to the new phenylthiomethylenation based upon thionium ion chemistry. We believe the two step conversion of the enol silyl ether of

cyclopentanone to the corresponding versatile β-phenylthiomethylidenecycloalkanone should be a general regiocontrolled approach.

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