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Ab initio and Semiempirical Corroboration of the Observed Stereoselectivity in the Transannular Diels-Alder Reaction Leading to Steroids

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Abstract: Various 14-membered macrocyclic trienes underwent transannular Diels-Alder reactions to yield tetracyclic structures that are stereoisomers of steroids. Due to the complexity of the effects at work during these reactions, a thorough molecular modeling study was carried out. Thus, some molecular mechanics, semiempirical and *ab initio* methods were compared and the results were finally used to rationalize the experimental results. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

The continuing interest in steroids stems from the wide range of pharmacological activity displayed by these extensively studied natural products. Needless to say, numerous approaches to their total synthesis have been successfully developed[1] and still, novel strategies are actively being pursued.[2] Our group recently reported transannular Diels-Alder cyclization of the trienes **A** and **B** which could be used to quickly build respectively the ABC and BCD ring systems of steroid (Figure 1).[3,4] Whereas independently Takahashi's group studied the cyclization of the triene **C**.[5] The reaction of **A** produced a 1:2 mixture of tricycles having the *cis-anti-trans* and *trans-anti-cis* geometry while the reaction of **C** gave only the *cis-anti-trans* geometry. Thus subtle effects influence the stereochemistry of the cycloaddition. In order to study this further we prepared substrates **D** with Z subtituents of differing sizes and studied their transannular Diels-Alder electrocyclization. For this purpose, our general convergent strategy was expected to meaningfully simplify the synthetic task at issue, as depicted in Figure 2. An added desirable advantage of this route includes the choice of connectors to be incorporated at a late stage in the synthesis, thereby offering insight as to the influence of increasing level of congestion at pro-C3 and C13 positions on the stereochemical outcome.

Each connector was found to influence the outcome of the key transannular Diels-Alder reaction. These reactions led to as many as three products resulting in difficult cases to rationalize in an empirical way *e.g.* by means of Dreiding models. Clearly reliable numerical modeling methods must be used and in fact these tricky problems represent a good test for today's transition state molecular calculations.

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[†] *We dedicate this paper to Prof. Yoshito Kishi on the occasion of his 60th birthday.*

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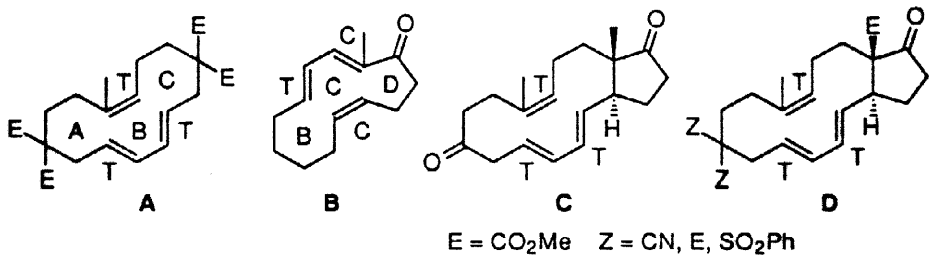


Figure 1. Various TADA precursors.

In the present work, we wish to report the synthesis and the transannular Diels-Alder reaction of macrocyclic trienes **25-27** (Scheme 3). We are also comparing the three following methods: 1) modeling with empirical force field, 2) semiempirical transition state location, and, 3) *ab initio* calculations. Then the most suitable theoretical technique together with the experimental results is used to rationalize all the factors governing the transannular Diels-Alder reactions of TTT trienic macrocycles like A (Figure 2).

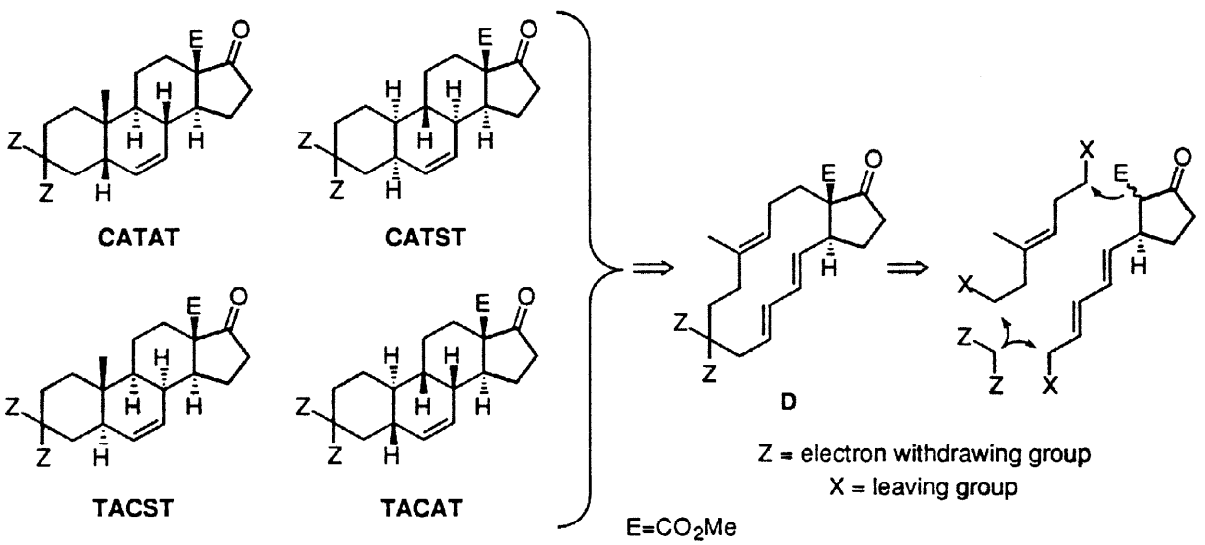


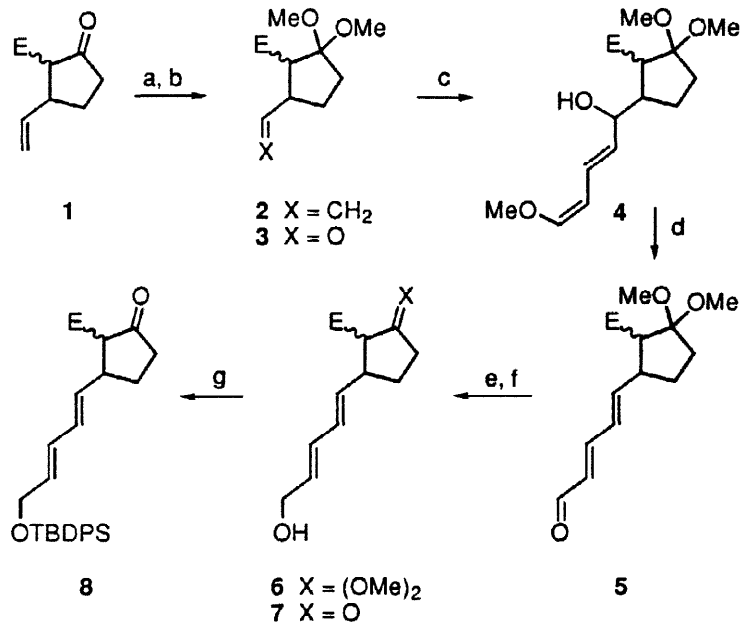
Figure 2. Retrosynthetic analysis.

Results and Discussion

Chemistry

Although the requisite dienophilic moiety has previously been prepared by our group,[6] we devised a more practical route, as illustrated in Scheme 1. Subjected to the action of methanol and trimethylorthoformate in the presence of *p*-toluenesulfonic acid, synthon **1**[7] gave the corresponding dimethoxyketal **2** as a 9:1 mixture of the *trans* and *cis* isomers respectively. Although possible, the separation was not of particular concern since the relative stereochemistry is inconsequential to the outcome (*vide infra*). Ozonolysis of this mixture under standard conditions proceeded smoothly providing the particularly stable aldehyde **3** in a combined yield of 89%. At this stage, we recognized that a four carbon chain extension of the aldehyde to the corresponding *E,E*-

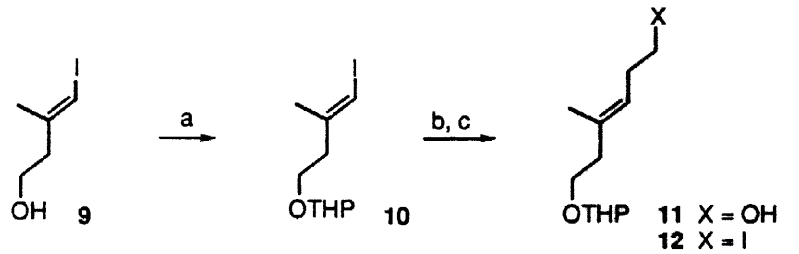
dienal homologue could afford a rapid entry to the requisite diene moiety. We were particularly attracted to the use of δ-methoxydienyl zirconocene chloride since its Grignard type addition to aldehydes followed by acidic treatment was reported to be highly stereoselective in providing *E,E*-dienals.[8] In the present case however, the presence of the dimethoxyketal unit on **4** precludes the use of highly acidic conditions necessary to complete the desired transformation. Thus, we reasoned that mesylation of the transient alcohol could achieve the same purpose via an *in situ* 1,6-elimination mediated by resident chloride ions. Indeed, these highly favorable conditions served to deliver dienal **5** of high isomeric purity (>95% *E,E* by NMR) in a combined yield of 71% from **3**. Once the homologation accomplished, it proved an easy matter to obtain an appropriately functionalized diene, first by sodium borohydride reduction of the aldehyde **5** to the corresponding alcohol **6**. Following hydrolytic cleavage of the ketal group, the alcohol **7** was protected as its TBDPS ether leading to the desired β-ketoester **8** set for coupling with the dienophilic moiety. The overall yield for the 7-step sequence from **1** was 61%.



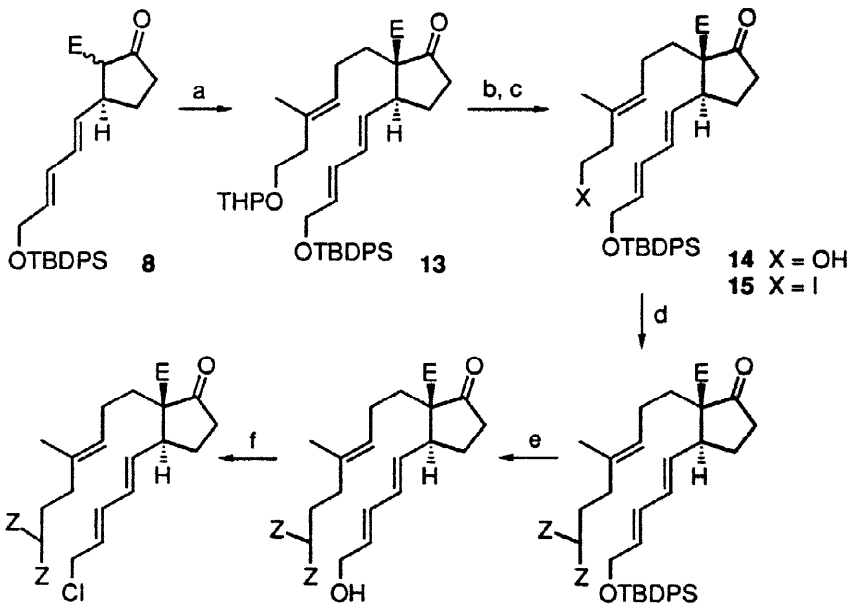
Scheme 1. (a) $CH(OMe)_3$, TsOH, MeOH, 40°C, 4 h, 91%; (b) O_3, $MeOH/CH_2Cl_2$ (1:5), -78°C ; PPh_3, -78°C to r.t., 98%; (c) *(Z)*-HC≡C-CH=CHOMe, $Cp_2Zr(H)Cl$, $AgClO_4$, CH_2Cl_2, r.t., 1 h; (d) MsCl, Et_3N, CH_2Cl_2, -30°C, 0.5 h, 71% (two steps); (e) $NaBH_4$, MeOH, -78°C, 0.5 h, 91%; (f) H_2O/HOAc (1:4), r.t., 1 h, 96%; (g) TBDPSCl, Imid, THF, r.t., 0.5 h, 90%. E=CO_2Me.

The dienophile **12** was readily synthesized in three steps from (*E*)-4-iodo-3-methyl-3-buten-1-ol **9**, which in turn was prepared from 3-butyn-1-ol via zirconium catalyzed carboalumination and subsequent iodinolysis.[9] Exposure of the alcohol **9** to dihydropyran in the presence of *p*-toluenesulfonic acid gave rise to the acetal **10**. Metallation of the vinylic iodide with *n*-butyllithium followed by ring opening of ethylene oxide provided the homoallylic alcohol **11**. Finally, the two carbon homologation sequence of the iodide **10** was completed through the conversion of the alcohol **11** to the corresponding halide **12** by a modified version of the Mitsunobu reaction using iodomethane as electrophile.[10] The overall yield for the 3-step sequence from **9** was 62%.

At the convergent step, the anion of ketoester **8** (Scheme 3) underwent coupling with iodide **12** exclusively from its less encumbered face providing a readily separable mixture of the desired compound **13** along



Scheme 2. (a) DHP, TsOH, CH_2Cl_2, 40°C, 0.5 h, 89%; (b) *i)* n-BuLi, Et_2O, -78°C, 0.5 h, *ii)* oxirane, -78°C to r.t., 82%; (c) PPh_3, DEAD, MeI, $PhCH_3$, r.t., 0.25 h, 85%.



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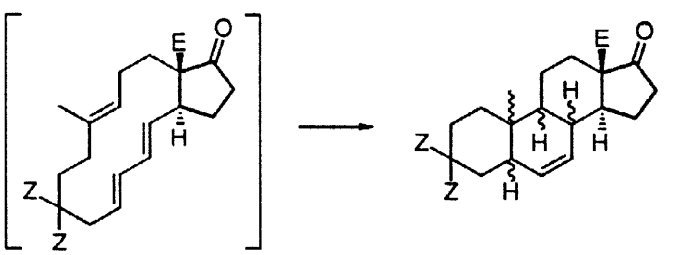
Z		compound (yield)		
CN	22 (86)	19 (78)	16 (97)
CO_2Me	23 (89)	20 (93)	17 (89)
SO_2Ph	24 (77)	21 (91)	18 (86)



	Z	TACAT	TACST	CATAT	CATST	ratio (yield)	entry
[25]	CN	28	29	30	31	4:1:2:0 (44)	1
[26]	CO_2Me	32	33	34	35	4:1:1:0 (46)	2
[27]	SO_2Ph	36	37	38	39	2:1:0:0 (65)	3

Scheme 3. (a) *i)* KH, $PhCH_3$, 0.5 h, r.t. *ii)* **12**, reflux, 10 h, 78%; (b) PPTS, *i*-PrOH, reflux, 3 h, 99%; (c) PPh_3, DEAD, MeI, $PhCH_3$, r.t., 0.25 h, 90%; (d) Z_2CH_2, NaH, DMF/THF (1:1), reflux, 1 h; (e) TBAF, THF, r.t., 2-24 h; (f) PPh_3, HCA, THF, 0°C, 0.5 h; (g) 12 h syringe pump addition over Cs_2CO_3 (5 eq), MeCN, +12h additional, reflux, final concentration: 1 μM, 44-46% (mixture of adducts).

with the corresponding *O*-alkylated adduct in 78% and 11% yield respectively. In preparation for the macrocyclization, the THP ether of **13** was cleaved by transacetalization with isopropanol and the resulting alcohol **14** was further transformed to the iodide **15** using the previous protocol. The stage was then set for the implementation of the requisite connectors, thus completing the carbon arrangement necessary for the construction of the steroids. Three sets of active hydrogen nucleophiles were incorporated, namely malononitrile, dimethyl malonate and bis(phenylsulfonyl)-methane in order to evaluate the influence of their increasing order of steric hindrance on the transition state. For this purpose, sodium hydride was used to generate the corresponding nucleophiles, all of which readily provided the macrocyclic precursors **16-18** upon treatment with iodide **15**. Following the removal of the silyl ethers under standard conditions, the resulting alcohols **19-21** were transformed to the allylic chlorides **22-24** using hexachloroacetone (HCA) and PPh_3.[11] The key step was then carried out by a 12 h syringe pump addition of the chlorides **22-24** over a refluxing suspension of cesium carbonate in acetonitrile, and in order to ensure completion of the cycloadditions, the mixtures were heated for an additional 12 h. Hence, the malononitrile and the dimethyl malonate precursors **22** and **23** each provided a mixture of TACAT, CATAT and TACST steroids in a 4:2:1 and 4:1:1 ratio respectively, while that of the *bis*-sulfone **24** led to the TACAT and TACST adducts in a proportion of 2:1. The ratios were determined by GC/MS (Hewlett Packard) and also by the relative intensity of the methyl signals in ^1H NMR. The major compounds were isolated from the mixtures by crystallization and their relative stereochemistry were unambiguously established by single crystal X-ray analysis of the malonate **32**.[12] The other major adducts **28** and **36** had similar NMR pattern as **32**. The stereochemistry of the minor adducts were empirically determined by multiplicity patterns of the olefinic protons in ^1H NMR. The TAC adducts typically give rise to a broad doublet (J ~ 9-10 Hz) and a doublet of triplet (J ~ 9-10 Hz and 3-3.5 Hz) whereas CAT adducts exhibit a broad doublet (10-12 Hz) and multiplet or doublet of doublet of doublet of doublet (J = 10.5, 2.5 Hz). Considering the unactivated nature of the diene and dienophilic partners, the second step of the overall process features soft reaction conditions beset only by the modest yield of macrocycles generated *in situ*. Competing dimerization and oligomerization arise from the rigidity of the desired macrocycles and accounts for the observed yields of adducts ranging from 44 to 65%.

Theoretical calculations

In order to untangle the subtle balance between substituent effects and tether ring conformations at the transition state level of our TADA reactions, several calculations had to be carried out. Despite the fact that transition-state modeling with empirical force fields met with success on several occasions in the past[13] and in particular with systems similar to ours,[4,14] the method proved sometimes awkward as correction factors must be added.[15] Also this method does not allow comparison between competing reactions of different types (e.g. DA, 1,5-H shift, ene, etc) and for this latter aspect, we became interested in molecular orbital calculations. As our systems were uncommonly large for accurate high level *ab initio* treatment, we have used the semiempirical AM1 hamiltonian at several occasions in the past.[16,17] This approach was successful in many instances, but difficulties were encountered when dealing with simple TTT systems (error of 1 kcal/mol).[18] The reason for the discrepancy between calculations and experimental results in this case is unknown, indicating that *ab initio* theory might be more appropriate to handle TTT systems (leading to [6.6.6] tricycles). As the molecules currently under investigation do possess such a trienic TTT system, *ab initio* calculations become relevant and in fact

necessary despite the large number of heavy atoms (17 without substituents). Each macrocycle can adopt several conformations, among which 4 may lead directly with little motion to the corresponding TACAT, TACST, CATAT and CATST transition states as displayed in Figure 3. The three non-isolated macrocyclic trienes **25-27** underwent a TADA reaction spontaneously during their formation. Although each of these precursors may collapse to 4 adducts, the CATST tetracycles **31**, **35** and **39** were never formed.

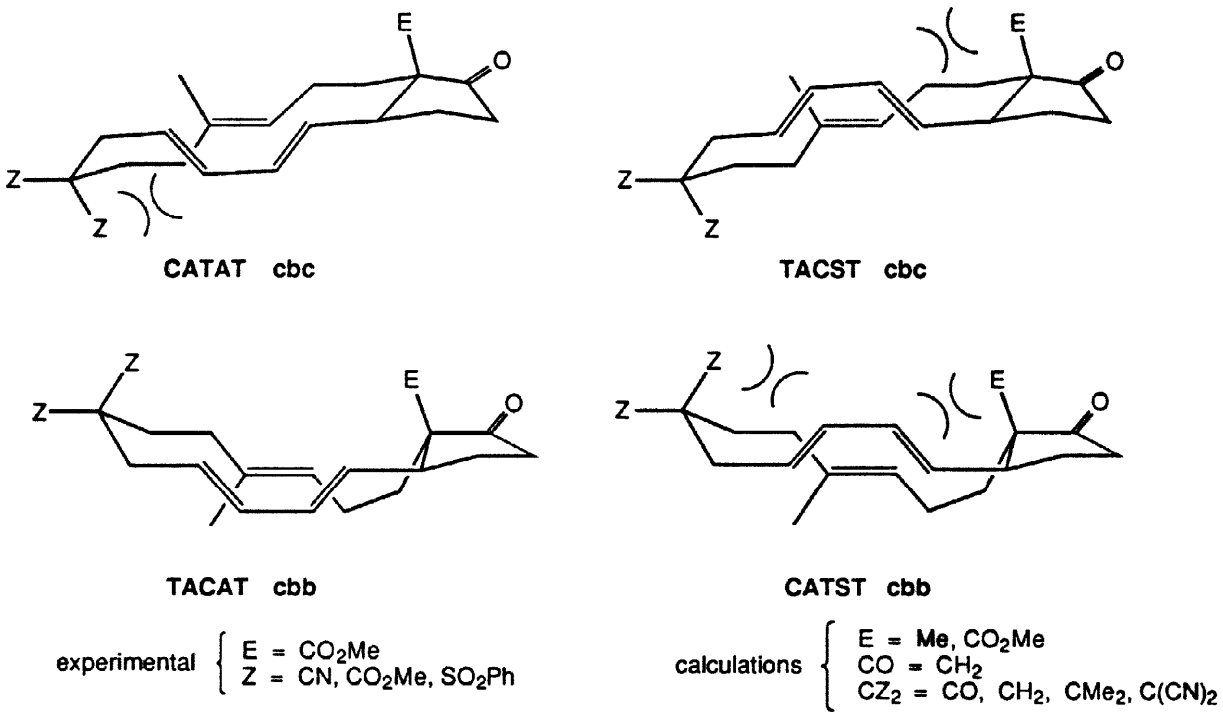


Figure 3. Transition-state-like geometries.

In order to simplify the systems to be modeled, the ester group E at the ring junction was replaced by a methyl group.[17] Contrary to a methyl ester group, a simple methyl group has virtually only one orientation which represents a major simplification since a tedious search for the most stable rotamer can be avoided. On top of this advantage, 3 heavy atoms were discarded from our already large systems. As a second simplification, the carbonyl unit in the 5-membered ring was replaced by a methylene group. The effect of the ketone on the outcome of the reaction should be marginal as it is far away from the reactive site. Finally, the connector CZ_2 group is increasingly bulky in the trienes **25-27** (Z = CN, CO_2Me, SO_2Ph). Apart from the cyano substituent, both other Z pendant groups are very large and also subject to rotational isomerism. Consequently a much simpler set of substituents was used during the calculations to probe the effect of increasing steric factors at the same ring position; (CZ_2 = CO, CH_2, CMe_2). The resulting 12 transition structures were localized at the semiempirical AM1[19] and PM3[20] levels within MOPAC 6.0[21,22] and *ab initio* 3-21G level[23] of theory within GAMESS[24,25] (Table 1).

As regards to geometrical features of our transition structures, the forming bond lengths increase gradually when issued from AM1, PM3, then 3-21G calculations. It is also noteworthy that these bond length values are longer in our macrocycle systems than those in the computed butadiene-ethylene transition structures. For

Table 1. Model theoretical studies.

CZ_2	TACAT cbb			TACST cbc			CATAT cbc			CATST cbb			basis	entry
	bonds a-b	rel E	pop	bonds a-b	rel E	pop	bonds a-b	rel E	pop	bonds a-b	rel E	pop	set	
C=O	2.16 2.14	3.18	1	2.17 2.12	3.15	1	2.18 2.11	0	98	2.20 2.08	5.57	/	AM1	4
	2.20 2.15	2.98	2	2.20 2.14	2.02	5	2.19 2.15	0	93	2.22 2.12	4.56	/	PM3	5
	2.24 2.25	4.62	/	2.25 2.24	4.02	/	2.26 2.22	0	100	2.26 2.21	7.54	/	3-21G	6
CH_2	2.16 2.13	2.74	2	2.17 2.12	2.92	2	2.18 2.10	0	96	2.20 2.08	5.89	/	AM1	7
	2.20 2.15	2.76	2	2.20 2.14	1.87	6	2.19 2.15	0	92	2.22 2.12	4.38	/	PM3	8
	2.24 2.25	2.93	1	2.26 2.23	2.32	4	2.27 2.22	0	95	2.26 2.21	7.02	/	3-21G	9
CMe_2	2.15 2.14	1.07	16	2.15 2.14	1.24	12	2.18 2.11	0	72	2.19 2.09	4.77	/	AM1	10
	2.19 2.15	1.49	8	2.19 2.15	0.53	29	2.18 2.15	0	63	2.21 2.13	3.73	/	PM3	11
	2.23 2.26	0.48	27	2.23 2.26	0	52	2.27 2.23	0.64	21	2.27 2.21	6.51	/	3-21G	12

Bond a (Å) refers to the forming bond 5-10 (steroid numbering) and bond b to the bond 8-9. Relative energies are in kcal/mol. The equilibrium Boltzmann populations are in %.

Table 2. Real case theoretical studies (see entry 1).

	TACAT			TACST			CATAT			CATST			basis	entry
	θ	rel E	pop	θ	rel E	pop	θ	rel E	pop	θ	rel E	pop	set	
rotamer 1	19.0	0	(36) 59	-124.2	1.55	(4) 6	16.6	0.37	(22) 35	35.9	4.10	(0) 0	AM1	13
rotamer 2	-147.4	0.39	(21)	43.6	1.80	(3)	-63.4	0.68	(14)	-132.1	4.36	(0)		
rotamer 1	12.1	1.29	(8) 13	-128.1	1.72	(4) 7	8.6	0	(46) 80	33.2	5.33	(0) 0	PM3	14
rotamer 2	-154.2	1.80	(4)	41.5	1.89	(3)	*6.6	0.19	(35)	-133.1	5.46	(0)		
rotamer 1	-14.4	0	57	-113.5	1.00	14	-20.4	0.48	29	50.7	5.41	0	3-21G	15
			57			14			29			0	exp	1

The population analyses were carried out at 80°C. Case 1 (figures in brackets): analysis on the eight possible transition state rotamers.
Case 2 (plain figures): analysis on four transition states, each being the major rotamer out of two for each possible Diels-Alder.
θ ester O=C-C(13)-C(14) dihedral angle.
* slightly different methyl rotamer.

example, the 3-21G mean value for our 12 systems is 2.24 Å, whereas the corresponding butadiene-ethylene bond length is 2.21 Å.[26] This could simply indicate that the transannular mode of reaction leads to an earlier transition state in comparison to its intermolecular counterpart.

In agreement with the experimental results, none of the theoretical methods predict the CATST adducts to be formed at all. Increasing the bulk of the CZ_2 group affects the TAC:CAT selectivity favoring the former. This is easily rationalized in terms of a pseudo 1,3-diaxial interaction between the Z sustituent and the CH diene group in the CAT transition states shown in Figure 3. This effect is most drastic at the 3-21G basis set. Indeed the 3-21G model seems to fare better than both semiempirical ones. Contrary to the experimental results, the CATAT product remains the major adduct according to AM1 and PM3 calculations.

However, even the more reliable 3-21 basis set wrongly predicts the TACST stereoisomer to be the most important adduct when the CZ_2 groups are large (e.g. CMe_2). In fact the TACAT compound was the major product in all the cases experimentally studied, and its quantity increases with the bulkiness of the CZ_2 groups. Clearly, our model does not reproduce correctly the experimental facts, probably because too many simplifications have been made. The methyl group on the key ring junction, initially meant to replace a methyl ester, was certainly the main culprit.

In order to ensure the reliability of the aforementioned theoretical figures, a real case was modelled. Since the most simple system is the macrocycle **25**, all its corresponding transition states had to be characterized (Table 2).

A survey of the ester rotamers was carried out with the semiempirical AM1 and PM3 hamiltonians. For each tetracyclic transition geometry, two rotamers were identified. Boltzmann distribution analyses (80°C) corresponding to reflux of acetonitrile considering either the eight transition states or the four most stable ester rotamer transition states (rotamers 1 only) gave practically the same results (largest error difference: 2%). For example, in the case of entry 13 (AM1 calculations), the former Boltzmann analysis yielded the following TACAT-TACST-CATAT-CATST product population: 57 (36+21) - 7 (4+3) - 36 (22+14) - 0 (0+0). The latter Boltzmann analysis gave the respective figures 59-6-37-0. Due to the close match between the two types of Boltzmann distributions, only the most stable rotamers were considered for 3-21G transition state localization. These 53-atom transition structures (27 heavy atoms) are displayed in Figure 4. Their corresponding energies predict exactly the right proportion of tetracycles experimentally observed. The AM1 hamiltonian leads also to fairly good results, despite its known inability to deal perfectly with TTT trienic systems leading to [6.6.6] tricycles. The PM3 calculations are basically irrelevant as they again favor the CATAT transition state. We have therefore demonstrated the efficacy of *ab initio* 3-21G calculations of transition structures to predict the selectivity in the transannular Diels-Alder reaction.

It is now clear that 3-21G *ab initio* calculations are superior over AM1 and PM3, semiempirical methods for this type of TTT system at least. Takahashi has also studied transannular Diels-Alder reactions of 14-membered TTT macrocyclic trienes.[14,15] He took the frozen STO-3G transition-structure geometry for the reaction of butadiene plus ethylene[27] and incorporated it into MM2. This method developed by Houk[28] proved successful in predicting the stereochemical outcome of a reaction closely related to the case exposed in entries 4, 5, and 6.[5] The only difference between Takahashi's molecule and these entries consists in a carbonyl group at the pro-17 position which has been replaced by a methylene group. Therefore, these two cases are close enough to be reasonably compared. In fact semiempirical AM1 (entry 4) and PM3 (entry 5) methods predict the CATAT

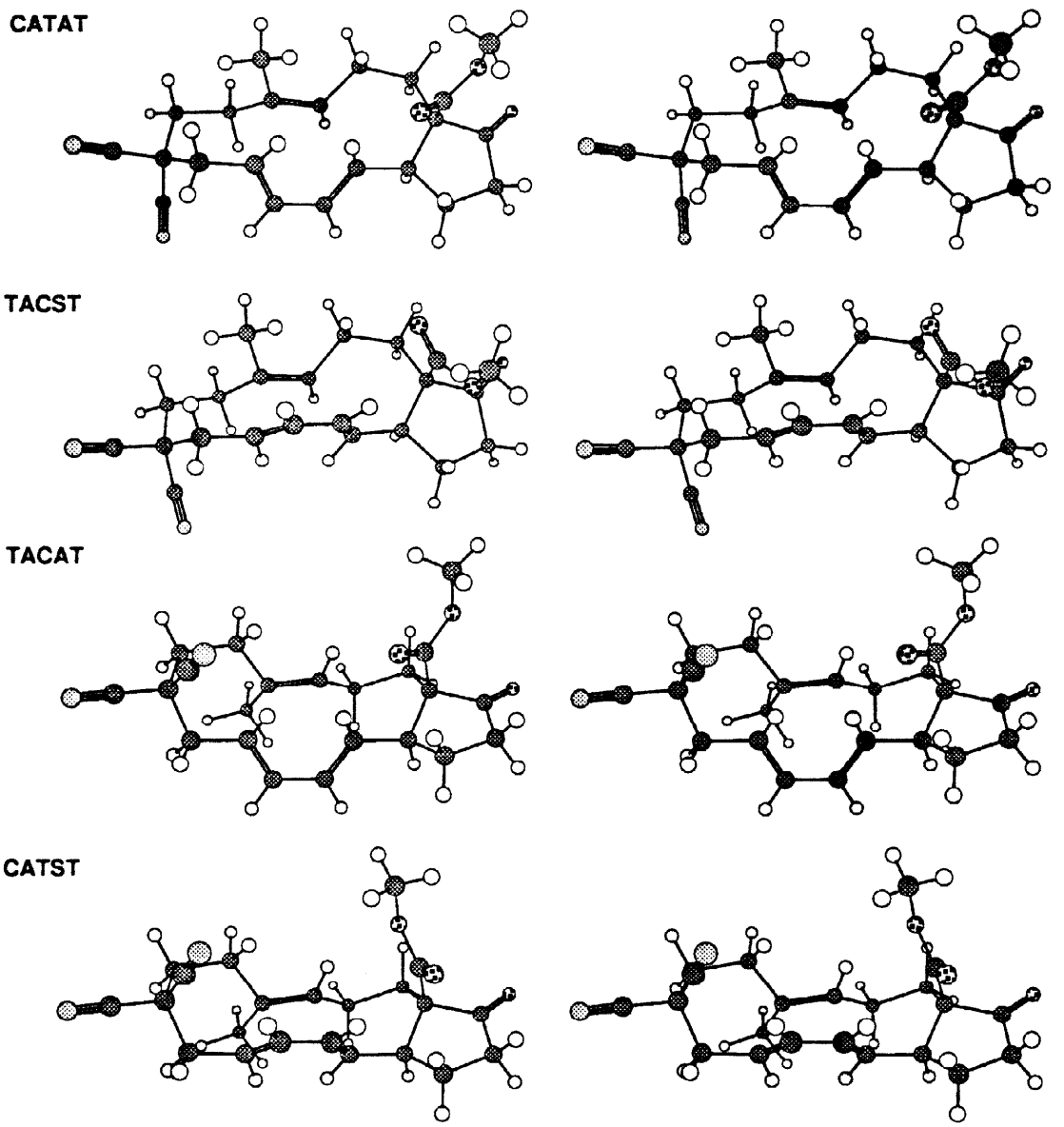
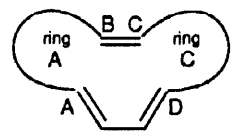


Figure 4. Entry 15 3-21G transition structures (stereoviews).

adduct to be the major product exactly as calculated by means of the empirical force field MM2. Again 3-21G calculations (entry 6) give a better fit with the experimental results since only the CATAT transition structure should be observed. It is noteworthy that the empirical MM2 method indicates that the TACST transition structure is 3.3 kcal/mol higher in energy than the CATAT transition structure.[5] Both these structures have chair-boat-chair (cbc) geometries. The chair-boat-boat (cbb) TACAT and CATST transition structures have much higher relative energies of 6.4 and 7.3 kcal/mol respectively. These figures demonstrate that the cbb transition geometry energies are overestimated by the empirical MM2 force field. Indeed replacement of the pro-3 sp^2 carbon atom by sp^3 centers leads to some TACAT adducts (entries 1, 2, 3, 9, 12) as found experimentally (Scheme 3) or theoretically (3-21G) calculated (Table 1). However, the TACAT MM2 transition state (pro-3 C=O) is so disfavored that introduction of a pro-3 sp^3 carbon is unlikely to overcome such an energy gap.

The reason why such a discrepancy might occur has been discussed by Houk, in what he called "twist mode asynchronicity".[29] Despite the fact that this effect was mostly present in the IMDA reaction of 1,3,8-nonatriene, it was also detected, although to a much smaller extent, in the 1,3,9-decatriene IMDA reaction. This effect showed up in the twisting motion of the reactants of about 10-15° in the former case. Inspection of some transition structure geometries (Table 3) indicates that the torsion α, which corresponds to the twisting motion of the diene and dienophile, is rather small for cbc geometries. Whereas, cbb geometries experience acute slanting between the AB and CD axes. It comes out that a rigid transition model based on ethylene and butadiene (α = 0) stands a good chance to yield rather good predictions for cbc transition state geometries, whereas it is not at all appropriate to correctly model cbb competing transition structures.

Table 3. TADA twist mode asynchronicity.



α = torsion ABCD

		CZ_2		
		C=O	$C(CN)_2$	
cbc	TACST	-5.0°	-4.4°	α
	CATAT	-0.3°	-7.6°	
cbb	TACAT	17.6°	14.3°	
	CATST	12.4	17.9°	

α Torsions are displayed for 3-21G optimized transition structures (entries 6 and 15 respectively).

Consequently, the use of molecular mechanics to deal with such complex systems can lead to unreliable results. Tandem QM/MM methods could be an alternative.[30] Semiempirical AM1 and PM3 methods also lead to inaccurate predictions.

Certainly, the full *ab initio* 3-21G saddle point location method is unbiased and represents the best way to model complicated cases like those exposed in the present work. Moreover, nowadays easy access to large computers allows this type of calculation to be carried out over relatively short periods.

Rationalization of the results

We wish now to use our calculations (Tables 1 and 2, entries 6, 9, 12, 15) and our experimental results (Scheme 3) to clarify further the effects of ring shape and substituent size at the pro-3 and 13 positions on the outcome of TADA of substrates like D (Figure 2).

The [6.6.6] tricyclic systems formed during the reaction adopt either a chair-boat-chair (cbc) or a chair-boat-boat (cbb) geometry at the transition state level (Figure 3). It has already been demonstrated that cbb

conformations are feasible as long as the boat-boat ring junction is *cis*.[31] On these grounds, the CATST adduct cannot be obtained. All three other transition states can theoretically exist. As the size of the CZ_2 connector at the pro-3 position increases, more TAC (TACAT and TACST) products are obtained. In fact, a very small CZ_2 group like a carbonyl leads only to CATAT adducts (entry 6), whereas a very large group at the same position like a bis-sulfone (entry 3) yields no CATAT products, but a mixture of TACAT and TACST products. This fact can be easily understood since the CATAT transition state displays a 1,3-diaxial interaction in the incipient A ring between one axial Z group and the diene. Thus, the size of Z controls the quantity of CATAT products.

Regarding the E group at the pro-13 position, it affects the CD bicyclic geometry (AT or ST). Increasing the size of the E group gives rise to a 1,3-diaxial interaction between itself and the diene in the incipient C ring of the ST adduct. This factor controls mainly the TACST:TACAT ratio, as the CAT:TAC ratio depends mostly on the CZ_2 group steric bulk. Two E groups have been considered, a methyl group (entries 9, 12) and a methyl ester group (entries 1, 2, 3, 15). The ester substituent appears to be bigger than the methyl counterpart in these cases as it leads to less TACST adduct. This is due to the fact that the C=O carboxyl bond tends to eclipse the C-C bond of the CD ring junction in the preferred rotamers (entry 15, TACAT angle -14.4°, CATAT angle: -20.4°); this preferred rotamer is impossible in a TACST geometry.

Finally, one may observe that for small CZ_2 groups like a carbonyl, both the CATAT and the TACAT transition state suffer similar steric hindrance. Nevertheless, the CATAT adduct is formed in this particular case (entry 6). Since the only difference between the two transition state geometries consists in the chair or boat conformation of the incipient C ring, it follows that the cbc conformation is definitely much preferred over its cbb counterpart.

Conclusion

The transannular Diels-Alder reaction represents a powerful tool as far as polycycle synthesis is concerned. Various natural steroids belonging to the CATAT family can be synthesized directly by this approach. Other potentially interesting non-natural steroids can also result from transannular Diels-Alder reaction. The selectivity of this reaction is highly dependent on the state of the tethers and on the steric effects of substituents at the transition state level. An experimental study coupled with molecular orbital calculations allowed us to expose the factors governing the diastereoselectivity. Large CZ_2 groups at position 3 favor TAC Diels-Alder adducts, while small CZ_2 groups at the same position lead mainly to CAT products. The E groups at position 13 induce selectivity at the CD bicyclic regions of the products. Large groups give mostly the TACAT over the TACST compounds, whereas small E groups behave in exactly the opposite way. In all the cases, the chair-boat-chair ABC ring arrangement is more stable than the chair-boat-boat geometry.

All the preceding factors may be additive in some cases or counteractive in others. It is usually impossible to accurately predict the result of these transannular Diels-Alder reactions unless precise calculations can be carried out. Indeed, we have demonstrated that such is the case since 3-21G *ab initio* calculations can correctly predict the selectivity of very complex examples. Whereas semiempirical methods performed rather poorly with these complicated cases. Indeed PM3 proved completely wrong (entry 14) and AM1 unreliable since it yielded results similar to 3.21G in some cases (entries 4, 7 and 13) and in full disagreement in other cases (entry 10).

Experimental

All reactions were performed under N_2 atmosphere with oven (150°C) or flame dried glassware. Et_2O and THF were dried by distilling over sodium/benzophenone ketyl. Toluene, CH_2Cl_2, and DMF were dried by distilling over CaH_2. Analytical TLC were carried out on glass plates precoated (0.25 mm) with silica gel 60 F-250 (Merck). The chromatograms were visualized under UV (254 nm) and/or by spraying with a solution of phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. Column chromatography was performed with flash silica gel 60 (230-400 mesh, Merck). All solvents used for chromatography were distilled. Melting points were recorded on a Reichert hot plate microscope and are reported uncorrected. IR spectra were taken on a Perkin-Elmer 1600 FT-IR spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 instrument. Chemical shifts are reported in δ units, parts per million from the $CHCl_3$ peak as internal reference (^1H: δ = 7.26, ^{13}C: δ = 77.0). Abbreviations used are: s singlet, d doublet, t triplet, q quadruplet, qn quintet, m multiplet, br broad. Mass spectral (MS) assays were obtained with a VG Micromass ZAB-2F spectrometer (70 eV).

2-Carbomethoxy-3-vinylcyclopentanone dimethylketal (2). A solution of 2-carbomethoxy-3-vinylcyclopentanone (10.4 g, 62.0 mmol) and trimethylorthoformate (19.7 g, 186 mmol) in methanol (100 mL) was treated with *p*-toluenesulfonic acid monohydrate (236 mg, 1.24 mmol) at 40°C for 1 h. The cooled solution was poured into 10% aqueous sodium bicarbonate (100 mL), then extracted with dichloromethane. Removal of solvent afforded an oil that was purified by flash chromatography (ethyl acetate / hexane, 1:9) to give the title compound as a clear oil (12.0 g, 91%); IR ($CHCl_3$) 3012, 2952, 1731, 1436, 1259, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) 5.72 (1H, ddd, J=7.5, 10.0, 17.0 Hz, C<u>H</u>=CH_2), 5.02 (1H, dt, J=1.5, 17.0 Hz, CH=CH<u>H</u> *trans*), 4.94 (1H, dt, J=1.5, 10.0 Hz, CH=C<u>H</u>H *cis*), 3.69 (3H, s, CO_2CH_3), 3.26, 3.18 (2x3H, 2s, $(OCH_3)_2$), 3.12 (1H, m, C<u>H</u>-CH=CH_2), 2.75 (1H, d, J=9.0 Hz, C<u>H</u>CO_2CH_3), 2.0-1.8 (3H, m, CH_2C<u>H</u>H), 1.51 (1H, m, CH_2CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 172.02, 140.02, 114.50, 111.44, 57.17, 51.67, 49.86, 48.72, 46.09, 36.20, 29.31; MS *m/e* 214 (M^+), 183 (M^+-OMe); HRMS calcd for $C_{11}H_{18}O_4$: 214.1205; found: 214.1200.

2-Carbomethoxy-3-formylcyclopentanone dimethylketal (3). Ozone was bubbled through a solution of ketal 2 (4.29 g, 20.0 mmol) in methanol (4 mL) and dichloromethane (20 mL) at -78°C until persistence of a bluish color. Triphenylphosphine (7.87 g, 30.0 mmol) was then added and the slurry was stirred 1 h at the same temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane, 3:7) to yield aldehyde **3** as a colorless oil (4.24 g, 98%); IR ($CHCl_3$) 3020, 2952, 1727, 1437, 1260, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) 9.57 (1H, s, CHO), 3.68 (3H, s, CO_2CH_3), 3.42 (1H, d, J=4.5 Hz, C<u>H</u>-CO_2CH_3), 3.20 (1H, m, C<u>H</u>-CHO), 3.19, 3.17 (2x3H, 2s, $(OCH_3)_2$), 2.13 (1H, m, CH_2-CH<u>H</u>), 2.0-1.8 (3H, m, C<u>H</u>$_2$-C<u>H</u>H); ^{13}C NMR ($CDCl_3$) 200.76, 172.00, 110.91, 52.62, 52.03, 50.58, 49.37, 48.67, 33.10, 22.57; MS *m/e* 216 (M^+), 187 (M^+-CHO); HRMS calcd for $C_{10}H_{16}O_5$: 216.0998; found: 216.0994.

2-Carbomethoxy-3-[(1*E*,3*E*)-5-oxopenta-1,3-dienyl]cyclopentanone dimethylketal (5). To an ice cold suspension of zirconocene chloride hydride (15.5 g, 60.0 mmol) in dichloromethane (80 mL) was added *cis*-1-methoxy-1-buten-3-yne (5.4 mL, 60 mmol) and the mixture was stirred at room temperature for 20 min. A solution of aldehyde **3** (4.32 g, 20.0 mmol) in dichloromethane (20 mL) was then added followed by

silver perchlorate (207 mg, 1.00 mmol). After 1 h, the reaction mixture was diluted with ether (100 mL), to which saturated sodium bicarbonate aqueous solution (200 mL) was added. The two phase mixture was stirred for 1 h then filtered. The organic layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was immediately diluted in dichloromethane (100 mL) and treated at -40°C with triethylamine (8.3 mL, 60 mmol) followed by methanesulfonyl chloride (3.1 mL, 40 mmol). After 30 min, saturated sodium bicarbonate aqueous solution (25 mL) was introduced and the mixture was slowly warmed to room temperature. The aqueous phase was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4) and evaporated. Purification of the residual oil by flash chromatography (ethyl acetate/hexane, 3:7) gave the *E,E*-dienal **5** (3.80 g, 71%, >95% isomeric purity by NMR) as a pale yellow oil; IR ($CHCl_3$) 3020, 2952, 1732, 1679, 1640, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) 9.50 (1H, d, J=8.0 Hz, CHO), 7.01 (1H, dd, J=10.5, 15.5 Hz, C<u>H</u>=CH-CHO), 6.30 (1H, dd, J=10.5, 15.0 Hz, CH-CH=C<u>H</u>), 6.12 (1H, dd, J=8.0, 15.0 Hz, CH-C<u>H</u>=CH), 6.06 (1h, dd, J=8.0, 15.5 Hz, CH=C<u>H</u>-CHO), 3.68 (3H, s, CO_2CH_3), 3.25 (3H, s, OCH_3), 3.20 (1H, m, C<u>H</u>-CH=CH), 3.17 (3H, s, OCH_3), 2.78 (1H, d, J=9.0 Hz, C<u>H</u>-CO_2CH_3), 2.0-1.8 (3H, m, C<u>H</u>$_2$-C<u>H</u>H), 1.56 (1H, m, CH_2-CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 193.64, 171.60, 151.87, 147.14, 131.03, 128.40, 111.39, 57.00, 51.95, 50.05, 48.81, 45.31, 36.02, 29.24; MS *m/e* 268 (M^+), 237 (M^+-OMe); HRMS calcd for $C_{14}H_{20}O_5$: 268.1311; found: 268.1307.

2-Carbomethoxy-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone dimethylketal (6). Sodium borohydride (643 mg, 17.0 mmol) was added at once to a solution of aldehyde **5** (3.98 g, 14.8 mmol) in methanol (100 mL) at -78°C. After 30 min, the mixture was warmed to 0°C and quenched with saturated aqueous ammonium chloride (10 mL). The methanol was removed under reduced pressure and the resulting aqueous solution was extracted several times with dichloromethane. Removal of the solvent from the dried (Na_2SO_4) organic extracts afforded the crude product which was purified by flash chromatography (ethyl acetate/hexane, 4:6) to yield alcohol **6** (3.62 g, 91%) as a colorless oil; IR ($CHCl_3$) 30.19, 2950, 1731, 1258, 1129, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) 6.16 (1H, ddt, J= 10.5, 15.0, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.05 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.74 (1H, dt, J=15.0, 6.0 Hz, CH=C<u>H</u>-CH_2), 5.57 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 4.13 (2H, brd, J=6.0 Hz, CH_2O), 3.68 (3H, s, CO_2CH_3), 3.25, 3.17 (2x3H, 2s, $(OCH_3)_2$), 3.10 (1H, m, C<u>H</u>-CH=CH), 2.73 (1H, d, J=9.0 Hz, C<u>H</u>CO_2CH_3), 2.0-1.8 (3H, m, C<u>H</u>$_2$C<u>H</u>H), 1.64 (1H, brs, OH), 1.48 (1H, m, CH_2CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 170.02, 135.95, 131.01, 129.49, 111.44, 63.15, 57.58, 51.78, 49.92, 48.75, 45.19, 36.21, 29.67; MS *m/e* 270 (M^+), 253 (M^+-OH); HRMS calcd for $C_{14}H_{22}O_5$: 270.1467; found: 270.1465.

2-Carbomethoxy-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone (7). A solution of ketal **6** (2.16 g, 8.00 mmol) in acetic acid (20 mL) and water (5 mL) was stirred at room temperature for 1 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate/hexane, 4:6) of the residue provided ketone **7** (1.71 g, 96%) as a colorless oil; IR ($CHCl_3$) 3611, 3467, 3021, 1756, 1727, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) 6.19 (1H, <u>A</u>BMX, J= 10.5, 14.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.13 (1H, A<u>B</u>Y, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.77 (1H, dt, J=14.5, 5.5 Hz, CH=C<u>H</u>-CH_2), 5.62 (1H, dd, J=7.5, 14.5 Hz, CH-C<u>H</u>=CH), 4.13 (2H, brd, J=5.5 Hz, CH_2O), 3.71 (3H, s, CO_2CH_3), 3.21 (1H, m, C<u>H</u>-CH=CH), 2.98 (1H, d, J=11.5 Hz, C<u>H</u>CO_2CH_3), 2.5-2.2 (3H, m, C<u>H</u>$_2$C<u>H</u>H), 1.94 (1H, brs, OH), 1.67 (1H, m, CH_2-CH<u>H</u>); ^{13}C NMR ($CDCl_3$)

210.59, 168.90, 133.36, 132.07, 130.62, 130.21, 62.87, 61.00, 52.40, 43.87, 37.94, 27.45; MS *m/e* 224 (M^+), 206 (M^+-H_2O); HRMS calcd for $C_{12}H_{16}O_4$: 224.1049; found: 224.1053.

2-Carbomethoxy-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (8). To an ice cold solution of alcohol **7** (2.87 g, 12.8 mmol) in dry tetrahydrofuran (80 mL) were successively added imidazole (2.17 g, 32.0 mmol) and *t*-butylchlorodiphenylsilane (4.0 mL, 15 mmol). After being stirred for 30 min at room temperature, the mixture was poured into saturated ammonium chloride aqueous solution and extracted with dichloromethane. Removal of the solvents from the dried extracts (Na_2SO_4) afforded an oil which was purified by flash chromatography (ethyl acetate/hexane, 2:8) to give the title compound **8** (5.33 g, 90%) as a clear oil; IR ($CHCl_3$) 3011, 2956, 2858, 1757, 1728, 1216, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75-7.7 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.33 (1H, ddt, J=10.5, 14.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.22 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.78 (1H, dt, J=14.5, 5.0 Hz, CH=C<u>H</u>-CH_2), 5.66 (1H, dd, J=7.5, 14.5 Hz, CH-C<u>H</u>=CH), 4.27 (2H, d, J=5.0 Hz, CH_2O), 3.77 (3H, s, CO_2CH_3), 3.28 (1H, m, C<u>H</u>-CH=CH), 3.06 (1H, d, J=12.0 Hz, C<u>H</u>CO_2CH_3), 2.5-2.2 (3H, m, CH_2C<u>H</u>H), 1.72 (1H, m, CH_2-CH<u>H</u>), 1.11 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 210.41, 168.90, 135.29, 133.32, 132.49, 132.11, 130.80, 129.49, 128.69, 127.51, 63.75, 60.99, 52.26, 43.87, 37.89, 27.45, 26.65, 19.08; MS *m/e* 462 (M^+), 431 (M^+-OMe); HRMS calcd for $C_{28}H_{34}O_4Si$: 462.2226; found: 462.2215.

(*E*)-1-Iodo-2-methyl-4-tetrahydropyranyloxy-1-butene (10). A solution of (*E*)-4-iodo-3-methyl-3-buten-1-ol (18.0 g, 85.0 mmol) and 3,4-dihydro-2*H*-pyran (11.6 mL, 128 mmol) in dichloromethane (250 mL) was treated with *p*-toluenesulfonic acid monohydrate (380 mg, 2.00 mmol) at 0°C for 30 min. Solid potassium carbonate was then added and the resulting suspension was stirred at room temperature for an additional 15 min. Filtration and evaporation of the solution gave an oil that was purified by flash chromatography (ethyl acetate/hexane, 1:9) providing iodide **10** (22.5 g, 89%) as a colorless oil; IR ($CHCl_3$) 3013, 2947, 1619, 1133, 1069, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) 5.97 (1H, m, J=1.0 Hz, CHI), 4.57 (1H, t, J=3.0 Hz, OCHO), 3.81 (2H, m, OC<u>H</u>$_2CH_2CH_2$), 3.47 (2H, m, OC<u>H</u>$_2CH_2C$=C), 2.49 (2H, t, J=7.0 Hz, CH_2C=C), 1.87 (3H, s, CH_3), 1.8-1.45 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$) 145.10, 98.66, 76.31, 65.31, 65.35, 62.22, 39.40, 30.58, 25.39, 24.26, 19.43; MS *m/e* 296 (M^+), 169 (M^+-I); HRMS calcd for $C_{10}H_{17}IO_2$: 296.0275; found: 296.0270.

(*E*)-6-Hydroxy-3-methyl-1-tetrahydropyranyloxy-3-hexene (11). *n*-Butyllithium (1.6 M in hexane, 50 mL, 75.0 mmol) was gradually added over 20 min to a solution of the vinylic iodide **10** (22.2 g, 75.0 mmol) in ether (100 mL) at -78°C. After an additional 30 min, condensed oxirane (13.2 g, 300 mmol) was transferred *via* canulla and the resulting heterogeneous mixture was allowed to warm to room temperature. The reaction was then poured into a saturated aqueous ammonium chloride aqueous solution, extracted with dichloromethane and dried (Na_2SO_4). Removal of the solvents under reduced pressure followed by flash chromatography (ethyl acetate/hexane, 4:6) afforded homoallylic alcohol **11** (13.2 g, 82%) as a colorless oil; IR ($CHCl_3$) 3620, 3010, 2946, 1442, 1386, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) 5.14 (1H, dt, J=7.0, 1.0 Hz, C=CH), 4.51 (1H, t, J=3.5 Hz, OCHO), 3.85-3.7 (2H, m, OC<u>H</u>$_2CH_2C$=C), 3.52 (2H, t, J=7.0 Hz, CH_2OH), 3.45-3.35 (2H, m, OC<u>H</u>$_2CH_2CH_2$), 2.38 (1H, brs, OH), 2.23 (2H, t, J=7.0 Hz, C=CC<u>H</u>$_2$), 2.21 (2H, q, J=7.0 Hz, C=CHC<u>H</u>$_2$), 1.61 (3H, t, J=1.0 Hz, CH_3), 1.8-1.4 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$) 135.17, 121.81, 98.63, 65.92, 62.25, 61.96, 39.61, 31.35, 30.51, 25.25, 19.49, 16.26; MS *m/e* 214 (M^+), 197 (M^+-OH); HRMS calcd for $C_{12}H_{22}O_3$: 214.1569; found: 214.1566.

(*E*)-6-Iodo-3-methyl-1-tetrahydropyranyloxy-3-hexene (12). To a solution of alcohol **11** (2.14 g, 10.0 mmol) and triphenylphosphine (3.42 g, 13.0 mmol) in toluene (60 mL) at room temperature were added rapidly and successively iodomethane (934 μL, 15.0 mmol) and diethyl azodicarboxylate (2.04 mL, 13.0 mmol). A pale yellow paste immediately separated from the organic solution. The latter was removed and the remaining salt was washed with toluene (10 mL). The combined toluene solutions were evaporated and flash chromatography (ethyl acetate/hexane, 2:8) of the residue provided iodide **12** (2.75 g, 85%) as a colorless oil; IR ($CHCl_3$) 3011, 2947, 2872, 1443, 1120, 1072, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) 5.14 (1H, tm, J=7.5, 1.0 Hz, C=CH), 4.57 (1H, t, J=3.5 Hz, OCHO), 3.77 (2H, m, $OC\underline{H}_2CH_2C{=}C$), 3.46 (2H, m, $OC\underline{H}_2CH_2CH_2$), 3.08 (2H, t, J=7.5 Hz, CH_2I), 2.56 (2H, q, J=7.5 Hz, $C{=}CHC\underline{H}_2$), 2.26 (2H, t, J=7.0 Hz, $C{=}CC\underline{H}_2$), 1.62 (3H, t, J=1.0 Hz, CH_3), 1.85-1.4 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$); ^{13}C NMR ($CDCl_3$) 135.11, 124.49, 98.57, 65.98, 62.13, 39.48, 32.24, 30.59, 25.35, 19.43, 16.61, 5.65; MS *m/e* 325 (MH^+), 223 (M^+-OTHP); HRMS calcd for $C_{12}H_{22}IO_2$ (MH^+): 325.0666; found: 325.0660.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-6-tetrahydropyranyloxy-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (13).** To an ice cold suspension of potassium hydride (345 mg, 8.60 mmol) in toluene (60 mL) was added a solution of β-ketoester **8** (3.80 g, 8.20 mmol) in the same solvent (20 mL). After the mixture had been stirred for 30 min at room temperature, a solution of iodide **12** (3.99 g, 12.3 mmol) in dry toluene (20 mL) was added and the reaction mixture was refluxed for 10 h. The mixture was then cooled to 0°C and a saturated aqueous ammonium chloride solution was added. The phases were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (ethyl acetate/hexane, 1:9) of the residual material gave the title compound (4.21 g, 78%) followed by the corresponding *O*-alkylated isomer (594 mg, 11%) as colorless oils; the title compound exhibited: IR ($CHCl_3$) 3014, 2954, 1749, 1729, 1113, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) 7.7-7.65 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.26 (1H, ddt, J=10.5, 14.5, 1.5 Hz, $C\underline{H}{=}CH\text{-}CH_2$), 6.15 (1H, dd, J=10.5, 14.5 Hz, $CH\text{-}CH{=}C\underline{H}$), 5.75 (1H, dt, J=14.5, 5.0 Hz, $CH{=}C\underline{H}\text{-}CH_2$), 5.56 (1H, dd, J=8.0, 14.5 Hz, $CH\text{-}C\underline{H}{=}CH$), 5.18 (1H, brt, J=7.0 Hz, C=CH), 4.59 (1H, t, J=3.5 Hz, OCHO), 4.23 (2H, d, J=5.0 Hz, CH_2OSi), 3.83 (2H, m, $OC\underline{H}_2CH_2C{=}C$), 3.65 (3H, s, CO_2CH_3), 3.47 (2H, m, $OC\underline{H}_2CH_2CH_2$), 2.90 (1H, q, J=8.0 Hz, $C\underline{H}\text{-}CH{=}CH$), 2.59 (1H, ddd, J=18.5, 5.0, 4.5 Hz, $CO\text{-}C\underline{H}H$), 2.27 (2H, t, J=7.0 Hz, $C\underline{H}_2\text{-}C(CH_3){=}CH$), 2.3-1.5 (13H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $C{=}CHC\underline{H}_2C\underline{H}_2$, $CO\text{-}CH\underline{H}\text{-}C\underline{H}_2$), 1.64 (3H, d, J=1.0 Hz, CH_3), 1.07 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 214.96, 170.28, 135.41, 133.44, 132.95, 132.10, 130.60, 129.56, 129.11, 127.57, 125.14, 98.58, 66.23, 63.94, 63.13, 62.15, 51.84, 48.04, 39.50, 38.36, 31.58, 30.63, 26.73, 26.06, 25.36, 22.67, 19.49, 19.14, 16.28; MS *m/e* 658 (M^+), 611 (M^+-*t*-Bu); HRMS calcd for $C_{40}H_{54}O_6Si$: 658.3689; found: 658.3685.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-6-hydroxy-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (14).** Pyridinium *p*-toluenesulfonate (113 mg, 450 μmol) was added to a solution of **13** (2.97 g, 4.50 mmol) in isopropanol (150 mL) and the reaction mixture was refluxed for 3 h. The solution was then cooled to room temperature and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (ethyl acetate/hexane, 3:7) to give alcohol **14** (2.55 g, 99%) as a clear oil; IR ($CHCl_3$) 3621, 3015, 2956, 1746, 1730, 1226, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) 7.7-7.65 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.27 (1H, ddt, J=10.5, 14.5, 1.5 Hz, $C\underline{H}{=}CH\text{-}CH_2$), 6.17 (1H, dd, J=10.5, 14.5 Hz, $CH\text{-}CH{=}C\underline{H}$), 5.75 (1H, dt, J=14.5, 5.0 Hz, $CH{=}C\underline{H}\text{-}CH_2$), 5.56

(1H, dd, J=8.0, 14.5 Hz, CH-CH=CH), 5.22 (1H, brt, J=6.5 Hz, C=CH), 4.24 (2H, d, J=5.0 Hz, CH_2OSi), 3.65 (5H, superimposed s and t, J=6.5 Hz, CH_2OH, CO_2CH_3), 2.89 (1H, q, J=8.0 Hz, CH-CH=CH), 2.59 (1H, ddd, J=18.5, 6.0, 5.5 Hz, CO-CHH), 2.23 (2H, t, J=6.0 Hz , CH_2-$C(CH_3)$=CH), 2.3-1.7 (7H, m, $C=CHCH_2CH_2$, CO-CHH-CH_2), 1.63 (3H, d, J=1.0 Hz, CH_3), 1.07 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 215.02, 170.22, 135.35, 133.37, 132.08, 130.43, 130.08, 129.52, 129.00, 127.51, 126.42, 63.88, 63.04, 60.05, 51.81, 48.07, 42.43, 38.24, 31.59, 26.67, 25.99, 22.67, 19.08, 15.66; MS *m/e* 574 (M^+), 517 (M^+-*t*-Bu); HRMS calcd for $C_{35}H_{46}O_5Si$: 574.3114; found: 574.3104.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-6-iodo-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (15).** To a solution of alcohol **14** (2.16 g, 3.80 mmol) and triphenylphosphine (1.29 g, 4.90 mmol) in toluene (38 mL) at room temperature were added rapidly and successively iodomethane (366 μL) and diethyl azodicarboxylate (772 μL). A pale yellow paste immediately separated from the organic solution. The latter was removed and the remaining salt was washed with toluene (10 mL). The combined toluene solutions were evaporated and a flash chromatography (ethyl acetate/hexane, 3:7) of the residue provided iodide **15** (2.33 g, 90%) as a colorless oil; IR ($CHCl_3$) 3010, 2957, 1746, 1732, 1234, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) 7.7-7.65 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.26 (1H, ddt, J=10.5, 14.5, 1.5 Hz, CH=CH-CH_2), 6.17 (1H, dd, J=10.5, 14.5 Hz, CH-CH=CH), 5.75 (1H, dt, J=14.5, 5.0 Hz, CH=CH-CH_2), 5.58 (1H, dd, J=8.5, 14.5 Hz, CH-CH=CH), 5.21 (1H, brt, J=6.0 Hz, C=CH), 4.25 (2H, d, J=5.0 Hz, CH_2OSi), 3.66 (3H, s, CO_2CH_3), 3.21 (2H, t, J=7.5 Hz, CH_2I), 2.90 (1H, q, J=8.5 Hz, CH-CH=CH), 2.60 (1H, m, CO-CHH), 2.52 (2H, t, J=7.5 Hz, CH_2-$C(CH_3)$=CH), 2.3-1.75 (7H, m, $C=CHCH_2CH_2$, CO-CHH-CH_2), 1.62 (3H, d, J=1.0 Hz, CH_3), 1.08 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 214.80, 170.26, 135.48, 134.42, 133.56, 132.24, 132.12, 130.62, 129.63, 129.20, 127.64, 126.45, 64.04, 63.20, 51.87, 48.27, 43.65, 38.36, 31.58, 26.79, 26.11, 22.81, 19.20, 15.29, 4.59; MS *m/e* 684 (M^+), 627 (M^+-*t*-Bu); HRMS calcd for $C_{35}H_{45}IO_4Si$: 684.2132; found: 684.2112.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-dicyano-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (16).** To an ice cold suspension of sodium hydride (60% in oil, 208 mg, 5.20 mmol) in *N,N*-dimethylformamide (20 mL) was added malononitrile (344 mg, 5.20 mmol). After 1 h of stirring at room temperature, a solution of iodide **15** (888 mg, 1.30 mmol) in dry tetrahydrofuran (20 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was then quenched with a saturated aqueous ammonium chloride solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane, 2:8) to yield the title compound (787 mg, 97%) as a colorless oil; IR ($CHCl_3$) 3028, 2955, 2860, 1750, 1730, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) 7.7-7.65 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.29 (1H, ddt, J=10.5, 14.5, 1.5 Hz, CH=CH-CH_2), 6.18 (1H, dd, J=10.5, 14.5 Hz, CH-CH=CH), 5.77 (1H, dt, J=14.5, 5.0 Hz, CH=CH-CH_2), 5.57 (1H, dd, J=8.5, 14.5 Hz, CH-CH=CH), 5.28 (1H, brt, J=7.0 Hz, C=CH), 4.21 (2H, d, J=5.0 Hz, CH_2OSi), 3.72 (1H, t, J=7.0 Hz, $CH(CN)_2$), 3.68 (3H, s, CO_2CH_3), 2.88 (1H, q, J=8.5 Hz, CH-CH=CH), 2.61 (1H, ddd, J=4.0, 6.0, 18.5 Hz, CO-CHH), 2.3-1.7 (11H, m, $CH_2CH_2C=CHCH_2CH_2$, CO-CHH-CH_2), 1.64 (3H, s, CH_3), 1.09 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 214.61, 169.95, 135.17, 133.23, 131.95, 131.43, 130.32, 129.39, 128.89, 127.39, 127.08, 125.90, 112.59, 63.74, 62.80, 51.66, 48.13, 38.06, 35.62, 31.40, 28.48,

26.55, 25.86, 22.50, 21.31, 18.90, 15.29 ; MS *m/e* 622 (M^+), 565 (M^+-*t*-Bu); HRMS calcd for $C_{34}H_{37}N_2O_4Si$ (M^+-*t*-Bu): 565.2522; found: 565.2517.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(carbomethoxy)-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (17).** To an ice cold suspension of sodium hydride (60% in oil, 240 mg, 6.00 mmol) in *N,N*-dimethylformamide (25 mL) was added dimethyl malonate (793 µL, 6.00 mmol). After 1 h of stirring at room temperature, a solution of iodide **15** (1.36 g, 2.00 mmol) in dry tetrahydrofuran (25 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was then quenched with a saturated aqueous ammonium chloride solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane, 2 :8) to yield the title compound (1.22 g, 89%) as a colorless oil; IR ($CHCl_3$) 3029, 2956, 1750, 1733, 1438, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) 7.7-7.65 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.24 (1H, ddt, J=10.5, 14.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.14 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.73 (1H, dt, J=14.5, 5.0 Hz, CH=C<u>H</u>-CH_2), 5.54 (1H, dd, J=8.5, 14.5 Hz, CH-C<u>H</u>=CH), 5.10 (1H, brt, J=7.0 Hz, C=CH), 4.21 (2H, d, J=5.0 Hz, CH_2OSi), 3.71 (6H, s, $CH(CO_2C\underline{H}_3)_2$), 3.63 (3H, s, CO_2CH_3), 3.32 (1H, m, C<u>H</u>$(CO_2CH_3)_2$), 2.87 (1H, q, J=8.5 Hz, C<u>H</u>-CH=CH), 2.57 (1H, ddd, J=4.0, 5.5, 18.0 Hz, CO-C<u>H</u>H), 2.3-1.7 (11H, m, $C\underline{H}_2C\underline{H}_2C$=CHC$\underline{H}_2C\underline{H}_2$, CO-CH<u>H</u>-C$\underline{H}_2$), 1.62 (3H, d, J=1.0 Hz, CH_3), 1.08 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 214.88, 170.22, 169.73, 135.37, 134.06, 133.42, 132.09, 130.52, 129.54, 129.03, 127.53, 124.94, 63.91, 52.33, 50.79, 48.08, 40.96, 38.30, 36.89, 31.58, 26.67, 26.01, 22.60, 19.11, 15.60; MS *m/e* 688 (M^+), 631 (M^+-*t*-Bu); HRMS calcd for $C_{40}H_{52}O_8$: 688.3431; found: 688.3419.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(phenylsulfonyl)-3-hexenyl]-3-[(1*E*,3*E*)-5-(*t*-butyldiphenylsiloxy)penta-1,3-dienyl]cyclopentanone (18).** To an ice cold suspension of sodium hydride (60% in oil, 512 mg, 12.8 mmol) in *N,N*-dimethylformamide (50 mL) was added bis(phenylsulfonyl)methane (3.79 g, 12.8 mmol). After 1 h of stirring at room temperature, a solution of iodide **15** (2.19 g, 3.2 mmol) in dry tetrahydrofuran (50 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was then quenched with a saturated aqueous ammonium chloride solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane, 2:8) to yield the title compound (2.35 g, 86%) as a colorless oil; IR ($CHCl_3$) 3028, 2956, 2860, 1731, 1449, 1330, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) 7.92 (4H, d, J=6.0 Hz, Ph), 7.7-7.5 (10H, m, Ph), 7.45-7.35 (6H, m, Ph), 6.31 (1H, dd, J=10.5, 15.0 Hz, C<u>H</u>=CH-CH_2), 6.19 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.78 (1H, dt, J=15.0, 5.0 Hz, CH=C<u>H</u>-CH_2), 5.57 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 5.12 (1H, brt, J=6.0 Hz, C=CH), 4.53 (1H, t, J=5.0 Hz, C<u>H</u>$(SO_2Ph)_2$), 4.25 (2H, d, J=5.0 Hz, CH_2OSi), 3.66 (3H, s, CO_2CH_3), 2.88 (1H, q, J=8.0 Hz, C<u>H</u>-CH=CH), 2.58 (1H, dt, J=18.5, 5.0 Hz, CO-C<u>H</u>H), 2.3-1.7 (11H, m, $C\underline{H}_2C\underline{H}_2C$=CHC$\underline{H}_2C\underline{H}_2$, CO-CH<u>H</u>-C$\underline{H}_2$), 1.33 (3H, s, CH_3), 1.08 (9H, s, *t*-Bu); ^{13}C NMR ($CDCl_3$) 214.51, 169.94, 137.84, 135.17, 134.17, 133.17, 132.86, 132.04, 129.38, 128.88, 128.45, 127.89, 127.39, 127.21, 80.80, 63.69, 62.82, 59.95, 51.64, 47.97, 38.09, 36.69, 31.65, 26.53, 25.91, 22.94, 22.44, 18.89, 14.66; MS *m/e* 852 (M^+), 795 (M^+-*t*-Bu); HRMS calcd for $C_{44}H_{47}O_8S_2Si$ (M^+-*t*-Bu): 795.2481; found: 795.2473.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-dicyano-3-hexenyl]-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone (19).** Tetrabutylammonium fluoride (1M in THF, 1.50 mL, 1.50 mmol) was added to an ice cold solution of silyl ether **16** (779 mg, 1.25 mmol) in tetrahydrofuran (15 mL) and the mixture was stirred a room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane, 1:1) to provide alcohol **19** (374 mg, 78%) as a colorless oil; IR ($CHCl_3$) 3613, 3026, 2954, 1750, 1730, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) 6.21 (1H, ddt, J=10.5, 13.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.13 (1H, dd, J=10.5, 13.5 Hz, CH-CH=C<u>H</u>), 5.77 (1H, dt, J=14.5, 6.0 Hz, CH=C<u>H</u>-CH_2), 5.56 (1H, dd, J=8.5, 14.5 Hz, CH-C<u>H</u>=CH), 5.22 (1H, brt, J=7.0 Hz, C=CH), 4.14 (2H, d, J=6.0 Hz, C<u>H</u>$_2$OH), 3.71 (1H, t, J=7.0 Hz, $CH(CN)_2$), 3.63 (3H, s, CO_2CH_3), 2.83 (1H, dt, J=10.0, 8.0 Hz, C<u>H</u>-CH=CH), 2.57 (1H, ddd, J=3.0, 7.0, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.7 (11H, m, C<u>H</u>$_2$C<u>H</u>$_2$C=CHC<u>H</u>$_2$C<u>H</u>$_2$, CO-CH<u>H</u>-C<u>H</u>$_2$), 1.59 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) 214.92, 170.13, 132.06, 131.87, 131.49, 131.28, 130.38, 127.40, 112.62, 62.94, 51.98, 48.32, 38.23, 35.76, 31.54, 28.72, 25.99, 22.63, 21.44, 15.45; MS *m/e* 384 (M^+), 366 (M^+-H_2O); HRMS calcd for $C_{22}H_{28}N_2O_4$: 384.2049; found: 384.2044.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(carbomethoxy)-3-hexenyl]-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone (20).** Tetrabutylammonium fluoride (1M in THF, 2.14 mL, 2.14 mmol) was added to an ice cold solution of silyl ether **17** (1.22 g, 1.78 mmol) in tetrahydrofuran (18 mL) and the mixture was stirred a room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane, 1:1) to provide alcohol **20** (743 mg, 93%) as a colorless oil; IR ($CHCl_3$) 3612, 3027, 2955, 1749, 1731, 1436, 1231 cm^{-1}; ^1H NMR ($CDCl_3$) 6.20 (1H, <u>A</u>BMX, J=10.0, 14.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.11 (1H, A<u>B</u>Y, J=10.0, 14.5 Hz, CH-CH=C<u>H</u>), 5.77 (1H, dt, J=14.5, 5.5 Hz, CH=C<u>H</u>-CH_2), 5.55 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 5.05 (1H, brt, J=6.5 Hz, C=CH), 4.13 (2H, d, J=5.5 Hz, CH_2OH), 3.68 (6H, s, $CH(CO_2C\underline{H}_3)_2$), 3.61 (3H, s, CO_2CH_3), 3.28 (1H, m, C<u>H</u>$(CO_2CH_3)_2$), 2.84 (1H, dt, J=8.0, 10.0 Hz, C<u>H</u>-CH=CH), 2.54 (1H, ddd, J=3.0, 6.5, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.65 (12H, m, C<u>H</u>$_2$C<u>H</u>$_2$C=CHC<u>H</u>$_2$C<u>H</u>$_2$, CO-CH<u>H</u>-C<u>H</u>$_2$, OH), 1.54 (3H, d, J=1.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 214.88, 170.16, 169.78, 134.08, 131.95, 131.73, 131.41, 130.38, 124.87, 63.08, 62.90, 52.34, 51.83, 50.79, 47.96, 38.24, 36.83, 31.52, 26.79, 25.96, 22.55, 15.55; MS *m/e* 450 (M^+), 432 (M^+-H_2O); HRMS calcd for $C_{24}H_{34}O_8$: 450.2253; found: 450.2244.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(phenylsulfonyl)-3-hexenyl]-3-[(1*E*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone (21).** Tetrabutylammonium fluoride (1M in THF, 3.26 mL, 3.26 mmol) was added to an ice cold solution of silyl ether **18** (2.32 g, 2.72 mmol) in tetrahydrofuran (30 mL) and the mixture was stirred a room temperature for 24 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/dichloromethane, 3:17) to provide alcohol **21** (1.52 g, 91%) as a colorless oil; IR ($CHCl_3$) 3607, 3026, 2954, 1731, 1448, 1330, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) 7.89 (4H, d, J=7.0 Hz, Ph), 7.67 (2H, t, J=7.0 Hz, Ph), 7.55 (4H, t, J=7.0 Hz, Ph), 6.23 (1H, dd, J=10.5, 14.5 Hz, C<u>H</u>=CH-CH_2), 6.14 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.79 (1H, dt, J=14.5, 5.5 Hz, CH=C<u>H</u>-CH_2), 5.57 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 5.07 (1H, brt, J=7.0 Hz, C=CH), 4.44 (1H, t, J=5.0 Hz, C<u>H</u>$(SO_2Ph)_2$), 4.14 (2H, d, J=5.5 Hz, CH_2OH), 3.65 (3H, s, CO_2CH_3), 2.84 (1H, q, J=8.0 Hz, C<u>H</u>-CH=CH), 2.58 (1H, ddd, J=3.0, 6.5, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.65 (11H, m, C<u>H</u>$_2$C<u>H</u>$_2$C=CHC<u>H</u>$_2$C<u>H</u>$_2$, CO-CH<u>H</u>-C<u>H</u>$_2$), 1.33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) 214.81, 170.13, 137.90,

134.43, 133.05, 132.18, 131.92, 131.31, 130.32, 129.33, 129.07, 127.27, 81.24, 62.95, 51.96, 48.20, 38.26, 36.94, 31.81, 26.05, 23.19, 22.62, 14.97 ; MS *m/e* 614 (M^+), 590 (M^+-H_2O); HRMS calcd for $C_{32}H_{38}O_8S_2$: 614.2008; found: 614.1993.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-dicyano-3-hexenyl]-3-[(1*E*,3*E*)-5-chloropenta-1,3-dienyl]cyclopentanone (22).** To an ice cold solution of alcohol **19** (50 mg, 130 µmol) and triphenylphosphine (51 mg, 195 µmol) in tetrahydrofuran (1 mL) was added hexachloroacetone (99 µL, 650 µmol) and the reaction was stirred for 30 min. The solvent was removed under reduced pressure and the residue was diluted with carbon tetrachloride (1 mL) and directly transferred to a silica gel column. Rapid flash chromatography (ethyl acetate/hexane, 3:7) provided allylic chloride **22** (45 mg, 86%) as a colorless oil; IR ($CHCl_3$) 3027, 2954, 1752, 1726, 1455, 1236 cm^{-1}; ^1H NMR ($CDCl_3$) 6.28 (1H, dd, J=10.5, 15.0 Hz, C<u>H</u>=CH-CH_2), 6.15 (1H, dd, J=10.5, 15.0 Hz, CH-CH=C<u>H</u>), 5.81 (1H, dt, J=14.5, 7.0 Hz, CH=C<u>H</u>-CH_2), 5.66 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 5.25 (1H, brt, J=7.0 Hz, C=CH), 4.10 (2H, d, J=7.0 Hz, $C\underline{H_2}Cl$), 3.69 (1H, t, J=7.0 Hz, $CH(CN)_2$), 3.67 (3H, s, CO_2CH_3), 2.85 (1H, dt, J=10.5, 8.0 Hz, C<u>H</u>-CH=CH), 2.61 (1H, ddd, J=3.0, 7.0, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.7 (11H, m, $C\underline{H_2}C\underline{H_2}C$=CHC$\underline{H_2}C\underline{H_2}$, CO-CH<u>H</u>-C$\underline{H_2}$), 1.61 (3H, s, CH_3): ^{13}C NMR ($CDCl_3$) 214.72, 170.09, 133.60, 133.24, 131.19, 128.26, 127.52, 112.58, 63.00, 52.12, 48.44, 44.90, 38.21, 35.87, 31.71, 28.84, 26.00, 22.75, 21.50, 15.53 ; MS *m/e* 402 (M^+), 366 (M^+-HCl); HRMS calcd for $C_{22}H_{27}N_2O_3Cl$: 402.1710; found: 402.1705.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(carbomethoxy)-3-hexenyl]-3-[(1*E*,3*E*)-5-chloropenta-1,3-dienyl]cyclopentanone (23).** To an ice cold solution of alcohol **20** (858 mg, 1.90 mmol) in hexachloroacetone (5 mL) was added triphenylphosphine (748 mg, 2.85 mmol) and the reaction was stirred for 30 min. The mixture was diluted with carbon tetrachloride (2 mL) and directly transferred to a silica gel column. Rapid flash chromatography (ethyl acetate/hexane, 1:9 then 3:7) provided allylic chloride **23** (797 mg, 89%) as a colorless oil; IR ($CHCl_3$) 3029, 2955, 1749, 1731, 1436, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) 6.25 (1H, dd, J=10.0, 14.5, 1.5 Hz, C<u>H</u>=CH-CH_2), 6.13 (1H, dd, J=10.0, 15.0 Hz, CH-CH=C<u>H</u>), 5.76 (1H, dt, J=14.5, 7.0 Hz, CH=C<u>H</u>-CH_2), 5.65 (1H, dd, J=8.0, 15.0 Hz, CH-C<u>H</u>=CH), 5.07 (1H, brt, J=6.5 Hz, C=CH), 4.08 (2H, d, J=7.0 Hz, CH_2Cl), 3.71 (6H, s, $CH(CO_2C\underline{H_3})_2$), 3.63 (3H, s, CO_2CH_3), 3.30 (1H, m, $C\underline{H}(CO_2CH_3)_2$), 2.87 (1H, dt, J=8.0, 10.5 Hz, C<u>H</u>-CH=CH), 2.57 (1H, ddd, J=3.0, 6.0, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.65 (11H, m, $C\underline{H_2}C\underline{H_2}C$=CHC$\underline{H_2}C\underline{H_2}$, CO-CH<u>H</u>-C$\underline{H_2}$), 1.56 (3H, d, J=1.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 214.55, 170.16, 169.78, 134.20, 133.65, 133.48, 131.01, 128.04, 124.84, 63.16, 52.40, 51.96, 50.86, 48.02, 44.91, 38.23, 36.93, 31.65, 26.86, 25.95, 22.65, 15.66; MS *m/e* 468 (M^+), 432 (M^+-HCl); HRMS calcd for $C_{24}H_{33}O_7Cl$: 468.1915; found: 468.1903.

[2*R,3*S**]-2-Carbomethoxy-2-[(*E*)-4-methyl-7,7-bis(phenylsulfonyl)-3-hexenyl]-3-[(1*E*,3*E*)-5-chloropenta-1,3-dienyl]cyclopentanone (24).** To an ice cold solution of alcohol **21** (183 mg, 300 µmol) and triphenylphosphine (118 mg, 450 µmol) in tetrahydrofuran (2 mL) was added hexachloroacetone (228 µL, 1.50 mmol) and the reaction was stirred for 30 min. The solvent was removed under reduced pressure and the residue was diluted with carbon tetrachloride (2 mL) and directly transferred to a silica gel column. Rapid flash chromatography (ethyl acetate/hexane, 1:9 then 4:6) provided allylic chloride **24** (148 mg, 77 %) as a colorless oil; IR ($CHCl_3$) 3028, 2956, 1731, 1448, 1331, 1235, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) 7.89 (4H, d, J=7.0 Hz, Ph), 7.66 (2H, t, J=7.0 Hz, Ph), 7.54 (4H, t, J=7.0 Hz, Ph), 6.26 (1H, dd, J=10.5, 14.5 Hz, C<u>H</u>=CH-CH_2), 6.13 (1H, dd, J=10.5, 14.5 Hz, CH-CH=C<u>H</u>), 5.76 (1H, dt, J=14.5, 7.0 Hz, CH=C<u>H</u>-

CH_2), 5.57 (1H, dd, J=8.0, 14.5 Hz, CH-C<u>H</u>=CH), 5.07 (1H, brt, J=7.0 Hz, C=C<u>H</u>), 4.44 (1H, t, J=5.0 Hz, C<u>H</u>$(SO_2Ph)_2$), 4.07 (2H, d, J=7.0 Hz, CH_2Cl), 3.65 (3H, s, CO_2CH_3), 2.85 (1H, q, J=8.0 Hz, C<u>H</u>-CH=CH), 2.58 (1H, ddd, J=3.0, 6.5, 18.5 Hz, CO-C<u>H</u>H), 2.3-1.65 (11H, m, $C\underline{H_2}C\underline{H_2}C$=CHC$\underline{H_2}C\underline{H_2}$, CO-CH<u>H</u>-C$\underline{H_2}$), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) 214.42, 169.95, 137.85, 134.36, 133.44, 133.24, 133.05, 131.00, 129.26, 129.00, 128.08, 127.14, 81.17, 62.94, 51.93, 48.03, 44.80, 38.12, 36.87, 31.77, 25.92, 23.12, 22.56, 14.90; MS *m/e* 596 (M^+-HCl); HRMS calcd for $C_{32}H_{36}O_7S_2$ (M^+-HCl): 596.1902; found: 596.1908.

3,3-Dicyano-18-methoxy-18-oxo-6-androsten-17-one (25). To a vigorously stirred suspension of cesium carbonate (375 μmol) in dry acetonitrile (70 mL) at reflux was added a solution of allylic chloride **22** (30 mg, 75 μmol) in the same solvent (5 mL) dropwise with a syringe pump over a 12 h period (final concentration = 1μM). After an additional 6 h of stirring at the same temperature, the mixture was allowed to cool to room temperature. The acetonitrile was evaporated and the residue was filtered over silica gel (ethyl acetate/hexane, 3:7) providing a mixture of TACAT (**28**), CATAT (**30**) and TACST (**29**) adducts (12 mg, 44%, 4:2:1 ratio); the major isomer **28** was crystallized from the mixture (m.p. 175-177°C, ethyl acetate / hexane and exhibited: IR ($CHCl_3$) 3020, 2956, 1750, 1724, 1209, 1164, 909 cm^{-1}; ^{1}H NMR ($CDCl_3$) 5.86 (1H, dt, J=10.0, 3.0 Hz), 5.35 (1H, dt, J=10.0, 2.0 Hz), 3.70 (3H, s), 2.96 (1H, m) 2.58 (1H, m), 2.35-1.85 (14H, m), 1.71 (1H, m), 1.39 (1H, dq, J=5.0, 13.5 Hz), 0.88 (3H, s); ^{13}C NMR ($CDCl_3$) 212.28, 169.32, 129.21, 127.35, 116.34, 115.18, 60.76, 52.34, 46.78, 42.51, 41.09, 37.08, 36.82, 35.20, 34.62, 33.20, 32.55, 30.35, 28.61, 23.04, 20.52, 14.31; MS *m/e* 366 (M^+), 334 (M^+-MeOH); HRMS calcd for $C_{22}H_{26}O_3N_2$: 366.1943; found: 366.1941. Compound **29** displayed: ^{1}H NMR ($CDCl_3$, selected data), 6.14 (brd, J = 9.5 Hz), 5.91 (dt, J = 10.0, 3.0 Hz), 0.74 (s); compound **30** exhibited: ^{1}H NMR ($CDCl_3$, selected data) 5.71 (brd, J = 10.5 Hz), 5.60 (m), 0.96 (s).

3,3-Bis(carbomethoxy)-18-methoxy-18-oxo-6-androsten-17-one (26). To a vigorously stirred suspension of cesium carbonate (1.63 g, 5.00 mmol) in dry acetonitrile (990 mL) at reflux was added a solution of allylic chloride **23** (469 mg, 1.00 mmol) in the same solvent (10 mL) dropwise with a syringe pump over a 12 h period (final concentration = 1μM). After an additional 6 h of stirring at the same temperature, the mixture was allowed to cool to room temperature. The acetonitrile was evaporated and the residue was filtered over silica gel (ethyl acetate/hexane, 1:9) providing a mixture of TACAT (**32**), CATAT (**34**) and TACST (**33**) adducts (198 mg, 46%, 4:1:1 ratio); the major isomer **32** was crystallized from the mixture (m.p. 150-153°C, ethyl acetate / hexane) and exhibited: IR ($CHCl_3$) 3026, 2956, 1726, 1438, 1246, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$) 5.73 (1H, dt, J=10.0, 3.0 Hz,), 5.35 (1H, dt, J=10.0, 2.0 Hz), 3.71, 3.68, 3.66 (3x3H, 3s), 2.85 (1H, m), 2.53 (1H, m), 2.3-1.55 (14H, m), 1.39 (1H, dt, J=5.5, 13.0 Hz), 1.12 (1H, dt, J=4.0, 14.5 Hz), 0.83 (3H, s); ^{13}C NMR ($CDCl_3$) 212.79, 172.68, 171.50, 169.44, 130.30, 127.51, 60.89, 55.16, 52.60, 52.11, 46.95, 43.10, 41.67, 37.24, 36.87, 35.32, 34.38, 31.77, 28.79, 26.61, 23.00, 20.58, 14.52; MS *m/e* 432 (M^+), 401 (M^+-OMe); HRMS calcd for $C_{24}H_{32}O_7$: 432.2148; found: 432.2141. Compound **33** displayed: ^{1}H NMR ($CDCl_3$, selected data) 5.99 (dt, J = 9.0, 3.5 Hz), 5.43 (brd, J = 9.0 Hz), 0.70 (s); compound **34** exhibited: ^{1}H NMR ($CDCl_3$, selected data) 5.64 (m), 5.57 (brd, J = 10.0 Hz), 0.81 (s).

3,3-bis(Phenylsulfonyl)-18-methoxy-18-oxo-6-androsten-17-one (27). To a vigorously stirred suspension of cesium carbonate (326 mg, 1.00 mmol) in dry acetonitrile (190 mL) at reflux was added a solution of allylic chloride **24** (127 mg, 200 μmol) in the same solvent (10 mL) dropwise with a syringe pump over

an 12 h period (final concentration = 1μM). After an additional 6 h of stirring at the same temperature, the mixture was allowed to cool to room temperature. The acetonitrile was evaporated and the residue was filtered over silica gel (ethyl acetate/hexane, 4:6) providing a mixture of TACAT (**36**) and TACST (**37**) adducts (78 mg, 65%, 2:1 ratio); the major isomer **36** was crystallized from the mixture (m.p. 223-224°C, acetate / hexane) and exhibited: IR ($CHCl_3$) 3026, 2957, 2883, 1747, 1723, 1448, 1312, 1234, 1149, 1076, 909 cm^{-1}; ^1H NMR ($CDCl_3$) 8.1-8.0 (4H, m, Ph), 7.75-7.55 (6H, m, Ph), 5.79 (1H, dt, J=10.0, 3.0 Hz), 5.35 (1H, brd, J=10.0 Hz), 3.69 (3H, s), 2.93 (1H, m), 2.87 (1H, m), 2.6-1.6 (15H, m), 1.39 (1H, dt, J=5.5, 13.5 Hz), 0.75 (3H, s); ^{13}C NMR ($CDCl_3$) 212.54, 169.33, 136.18, 134.52, 131.60, 131.15, 128.76, 128.52, 128.31, 87.81, 60.89, 52.22, 46.91, 42.41, 39.28, 37.34, 36.82, 34.88, 33.65, 31.52, 28.80, 27.32, 23.04, 22.85, 22.59, 20.71, 13.92; MS *m/e* 596 (M^+); HRMS calcd for $C_{32}H_{36}O_7S_2$ (M^+): 596.1902; found: 596.1908. Compound **37** displayed: ^1H NMR ($CDCl_3$, selected data) 6.06 (brd, J = 9.0 Hz), 5.56 (dt, J = 9.0, 3.5 Hz), 0.62 (s).

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