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TANDEM [4+2]/[3+2]-CYCLOADDITIONS. 2. ASYMMETRIC INDUCTION WITH A CHIRAL VINYL ETHER†

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Abstract: A tandem [4+2]/[3+2]-cycloaddition of nitroalkenes tethered to α,β-unsaturated ester dipolarophiles can be effectively triggered with a vinyl ether. Using the chiral vinyl ether **6** as the dienophile, nitroalkenes **1** and **2** undergo highly selective tandem cycloaddition. Hydrogenolytic cleavage of the resulting nitroso acetals produce α-hydroxy lactams (-)-**14** and (-)-**21** in >98% e.e. with excellent recovery of the chiral auxiliary. The high diastereoselectivity is seen to arise from a strong endo preference for the vinyl ether together with an intrinsic facial bias in the auxiliary.

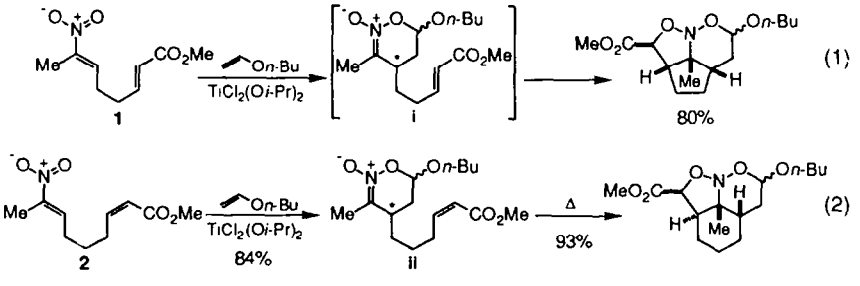
INTRODUCTION

The enormous power and utility of the Diels-Alder reaction for the stereoselective construction of both cyclic and acyclic compounds continues to inspire synthetic organic chemists. In recent years, a considerable effort has been directed toward the development of asymmetric variations using chiral-auxiliary-modified dienes and dienophiles.[1] Moreover, exciting advances in asymmetric cycloadditions employing chiral catalysts are now on record.[2]

Within the vast subclass of heteroatomic [4+2]-cycloadditions,[3] asymmetric modifications have also been developed. Among the various feasible permutations, several are noteworthy: 1) chiral heterodienes[4] with achiral dienophiles, 2) chiral heterodienophiles[5] with achiral dienes, 3) chiral dienophiles[6] with achiral heterodienes 4) chiral dienes and achiral heterodienophiles (with and without chiral catalysts)[7a] and 5) achiral dienes and achiral heterodienophiles using chiral lanthanide,[7] main group,[8] and transition-metal catalysts.[9]

Our interest in asymmetric, heterodiene Diels-Alder reactions is part of an ongoing program on the cycloaddition chemistry of nitroalkenes.[10] Recently, we reported the tandem [4+2]/[3+2]-cycloaddition of functionalized *E*-nitroalkenes with olefins and enol ethers.[11] These reactions, readily promoted by a mild Lewis acid, were successful with both di- and trisubstituted nitroalkenes. The substrates studied incorporated either α,β-unsaturated ester or α,β-unsaturated nitrile dipolarophiles appended by two- or three-atom tethers. The tandem cycloaddition of nitroalkenes **1** and **2** with *n*-butyl vinyl ether are exemplary, Scheme I.

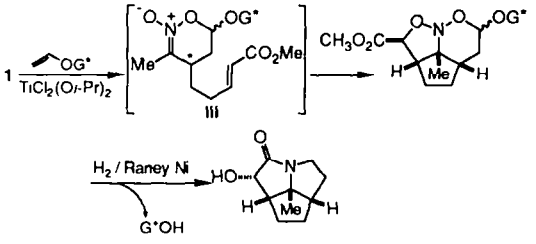
Scheme I



†Dedicated to Professor W. David Ollis on the felicitious occasion of his 65th birthday.

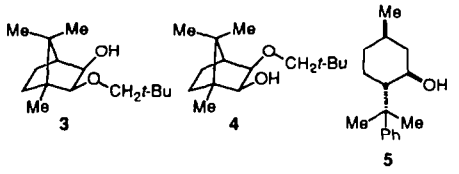
The stereoselectivities of the tandem cycloadditions are remarkable. Starting from simple, acyclic, achiral precursors, the reaction produces three rings and five stereogenic centers in one manipulation.[12] The anomeric center notwithstanding, the reactions proceed with >100:1 (eq 1) and >30:1 (eq 2) overall stereoselectivity! Scheme I shows that of the five new centers, two are produced in the [4+2]-cycloaddition and three are produced in the [3+2]-process. From our previous studies it is clear that the creation of the latter three centers is controlled by three factors: 1) the configuration of the extant nitronate center (*), 2) the tether length and 3) the dipolarophile configuration. Thus, the design of an asymmetric variant of this reaction must involve the selective construction of that nitronate stereocenter from which the other centers evolve. We, therefore, focused our efforts on the development of an auxiliary-based (G*), chiral vinyl ether with exquisite enantioface-selective properties for the nitroalkene, Scheme II.[13] This approach takes full advantage of the hydrogenolytic unmasking of the nitroso acetal to release the chiral auxiliary G*OH in recoverable form.

Scheme II



Chiral vinyl ethers have been employed in asymmetric Diels-Alder reactions,[14] Bradsher cycloadditions[6a] and ketene [2+2]-cycloadditions[15] with varying levels of stereoselectivity. For a preliminary survey of structural types, we selected the three chiral alcohols **3**-**5** available in scalemic form by established procedures from (+)-camphor[16] (to **3** and **4**) or (+)-pulegone[17] (to **5**). This report will disclose the remarkably high selectivity obtainable in the tandem cycloaddition of nitroalkenes **1** and **2** with a chiral vinyl ether and analyze the origin of that selectivity.

Chart I

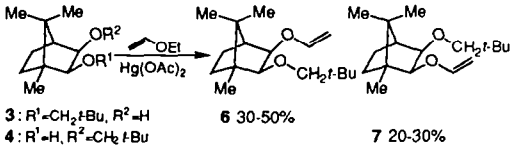


RESULTS

A. PREPARATION OF CHIRAL VINYL ETHERS

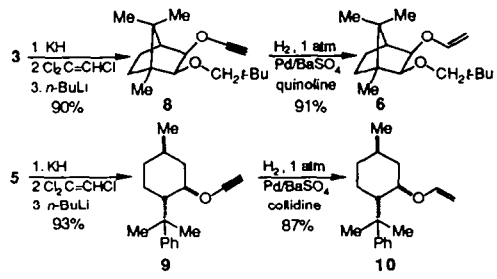
All of the cycloadditions described below employed simple unsubstituted vinyl ethers derived from the alcohols **3**, **4** and **5**. The synthesis of these alcohols was readily achieved following the literature descriptions.[16,17] The preparation of the requisite vinyl ethers was first accomplished by mercury-catalyzed vinyl exchange with vinyl acetate or ethyl vinyl ether.[18] This classic approach was only moderately successful providing **6** from **3** in 30-50% yield and **7** from **4** in 20-30% yield, Scheme III.

Scheme III



Superior methods for the preparation of alkenyl ethers have recently been reported by Greene, specifically to access chiral ketenophiles.[19] In this procedure, potassium alkoxides are treated with trichloroethylene to produce dichloro enol ethers which are dechlorinated *in situ* with *n*-butyllithium. The alkoxyalkynyllithiums can be protonated or alkylated, and the acetylenic ethers further reduced. Thus, the acetylenic ether **8** was prepared from **3** in 90% yield after simple protonation. Semi-hydrogenation of **8** with $Pd/BaSO_4$ and quinoline produced **6** in 91% yield, Scheme IV. The ratio of $Pd/BaSO_4$ to quinoline was crucial to suppress saturation to an ethyl ether. Surprisingly, the isomeric alcohol **4** failed to react with trichloroethylene, presumably due to steric hindrance. Fortunately, **7**, only available from vinyl exchange, was the less efficacious auxiliary. The third chiral alcohol examined, 8-phenylmenthol (**5**) was converted to the required vinyl ether **10** by the Greene procedure in good yield, Scheme IV.

Scheme IV



The nitroalkene substrates **1** and **2** were prepared by *E*-[20a] or *Z*-selective[20b] olefination of 1,4- and 1,5-dialdehyde **11**[21a] and **12**[21b] equivalents followed by standard nitroolefination,[22] Scheme V. Full description of the synthesis of these compounds will be reported elsewhere.

B. TANDEM CYCLOADDITION WITH 1

In the preliminary studies of tandem cycloaddition with **1** and *n*-butyl vinyl ether[11] the optimized reaction protocol employed 5 equivalents of the dienophile. Clearly, this is unacceptable for a precious chiral reagent. Thus, our first objective was the reoptimization of the reaction using vinyl ether **6**. In addition to minimizing the amount of **6**, the variable anomer composition of the cycloadducts had to be addressed. Specifically, this ratio reflects the exo/endo preference of the dienophile (if kinetically controlled) and has obvious consequences on the extent of diastereoselectivity.

1. Optimization of Reaction Conditions. The selection of the optimal Lewis acid was based on a brief survey of logical candidates. Dichlorotitanium diisopropoxide ($TiCl_2(Oi\text{-}Pr)_2$) was the only reagent examined previously, following the Seebach procedure.[12a] Disappointingly, none of the other Lewis acids examined ($BF_3{\cdot}OEt_2$, $ZnCl_2$, $MgBr_2{\cdot}OEt_2$, $SiCl_4$ or $TiCl(Oi\text{-}Pr)_3$) induced the reaction between **1** and **6**, only destruction of the vinyl ether was observed with recovery of **1** and **3**. Thus, $TiCl_2(Oi\text{-}Pr)_2$ remained the reagent of choice.

Establishing the optimum conditions for consumption of the nitroalkene was examined next. The most representative of many experiments are collected in Table 1. In all experiments, a solution of $TiCl_2(Oi\text{-}Pr)_2$ reagent was freshly prepared, added to a cold solution of the nitroalkene, followed by addition of **6** at -78°C. Ideally, only one equivalent of **6** should be used and our initial experiments employed this stoichiometry varying the amount of Lewis acid, time and temperature (entries 1-7). For significant conversion of the nitroalkene at least 1.5 equiv of $TiCl_2(Oi\text{-}Pr)_2$ (based on vinyl ether) was needed; the highest yields obtained with 2.0-2.5 equiv of $TiCl_2(Oi\text{-}Pr)_2$. Nonetheless, unreacted nitroalkene always remained when only one equiv of **6** was used. Extended reaction times and elevated temperatures had little effect on the yield of cycloadducts **13** (compare entries 3 and 4). Therefore, it appeared that the incomplete conversion of **1** resulted not from slow reaction, but from a competitive, Lewis-acid-catalyzed destruction of **6** (**3** was always detected during reaction). Accordingly, the amount of the dienophile was increased. With as few as 1.2 equiv of **6** the nitroalkene was almost completely consumed. The use of larger quantities of the dienophile led to diminishing returns, though still affording up to an 80% yield on a 1 mmol scale. Thus, the conditions of entries 8 or 9 represent the optimized protocol.

Scheme V

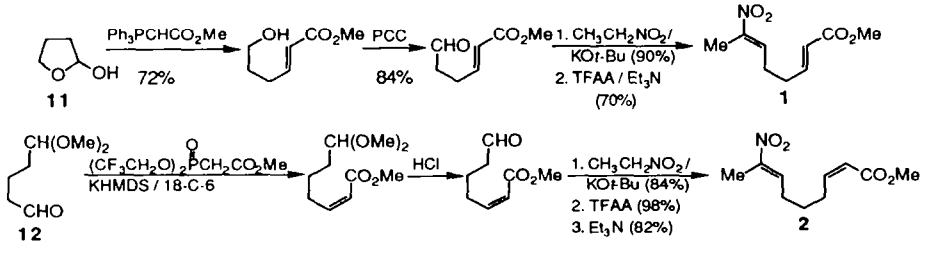
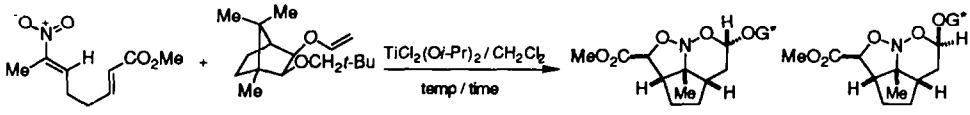


Table 1. Optimization of Stoichiometry.[a]



1 6 13a 13b

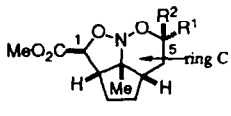
entry	vinyl ether (6), equiv[b]	$TiCl_2(Oi\text{-}Pr)_2$, equiv[b]	temp, °C	time, h	yield, %[c]	13a/13b[d]
1	1	1.5	-78	2.5	75	2.6/1
2	1	1.5	-78(-60)(-20)	24(2)(2)	60	1.9/1
3	1	2.0	-78	2	78	40/1
4	1	2.0	-78(20)	24(2)	81	1.6/1
5	1	2.0	-78	20	e	4.4/1[e]
6	1	2.5	-78	20	e	4.7/1[e]
7	1	3.0	-78	20	e	4.5/1[e]
8	1.2	2.2	-78	4	e	100/1[e]
9[f]	1.2	2.4	-78	22.5	82(89)[g]	4.2/1[h]
10	1.2	3.0	-78	8	94	17/1
11	1.5	3.0	-78	24	78	13/1
12	1.5	3.0	-78	24	86	-

[a]All reactions run in CH_2Cl_2 solution at 0.17-0.21 M. [b]Based on **1**. [c]Combined yield of separated isomers. [d]Ratio of isolated isomers. [e]Analytical scale, ratio determined by ^1H NMR. [f]Preparative (1 mmol) scale. [g]Yield based on conversion, 8% of **1** recovered. [h]Trace of **13c** (0.3%) detected.

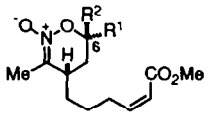
Throughout the optimization studies, the ratio of **13a** to **13b** was variable. Under all conditions, the α-isomer **13a** was predominant, the largest excesses observed at low temperature with shorter reaction times (entries 3 and 8). The relative proportion of the β-isomer **13b** increased if the reaction was allowed to warm (entries 2 and 4) or was kept at -78°C for longer periods (entries 5-7 and 9). Thus, it appeared that the α-isomer is favored both kinetically and thermodynamically, although the kinetic preference is considerably greater. Control experiments with both **13a** and **13b** established that these products *do not interchange* under the reaction conditions. Circumstantial evidence suggests that the [3+2]-cycloaddition does not occur at low temperature (<0°C), implying that the epimerization takes place at the level of the nitronate **i**, Scheme I. As will become evident from the degradation studies (*vide infra*), the anomeric composition is inconsequential to the stereochemical outcome. Nonetheless, establishing the configuration at the anomeric center is crucial for reconstructing the preferred transition structure.

The overall stereostructure of **13** is assured by X-ray crystallographic analysis of the tandem cycloadduct from 2,3-dimethyl-2-butene.[11] In the vinyl ether series (Scheme I), two isomeric nitroso acetals were produced which were independently transformed to the same tricyclic lactam thus establishing their epimeric relationship uniquely at C(5). The assignment of configuration at the anomeric center in **13** is based on analysis of the ^1H NMR chemical shift and coupling pattern of HC(5). The critical spectroscopic data collected in Table 2 convincingly show a correlation between the major and minor cycloadducts from **1** with **6** and with *n*-butyl vinyl ether.[11] This correspondence also holds for the cycloadducts from **2** (*vide infra*). The analysis of the coupling patterns in **13a** and **13b** is complicated by the preference for a boat conformation of ring C due to the ring fusion constraints.[23] However, in the

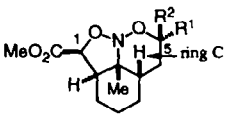
Table 2. Selected Spectroscopic Data for Nitroso Acetals and Nitronates



13



18



19

structure	R^1 [a]	R^2 [a]	X_n [b]	^{1}H NMR (ppm, Hz)		^{13}C NMR (ppm)
				δHC(5)[c] or HC(6)[d]	m[e]; $J_{5,6}$ m[e]; $J_{5,6}$	δC(5)[c] or C(6)[d]
13a	OG*	H	major	5.10	dd; 6.3, 2.6	100.79
13b	H	OG*	minor	5.12	t; 7.3	96.01
13c	H	OG*	trace[f]	4.97	t; 7.4	
g	O*n*-Bu	H	major	5.08	dd; 6.4, 3.5	99.65
g	H	O*n*-Bu	minor	4.94	t; 7.4	98.62
18a	OG*	H	major	5.25	t; 3.5	102.48
18b	H	OG*	minor	5.45	brs	98.78
18c	OG*	H	trace[h]	5.36	t; 4.6	
g	O*n*-Bu	H	major	5.24	t; 4.2	102.40
g	H	O*n*-Bu	minor	5.25	t; 2.6	101.04
19a	OG*	H	major	4.61	dd; 9.5, 1.8	100.16
19b	H	OG*	minor	5.09	br d; 3.5	96.65
19c	OG*	H	trace[h]	4.78	dd; 9.9, 1.6	
g	O*n*-Bu	H	major	4.66	dd; 9.9, 2.0	99.88
g	H	O*n*-Bu	minor	4.91	br d; 3.5	99.44

[a]G*OH = 3. [b]Fraction in mixture. [c]For nitroso acetals. [d]For nitronates. [e]Multiplicity HC(5)/(6). [f]0.3%. [g]From ref. 11. [h]2.2%.

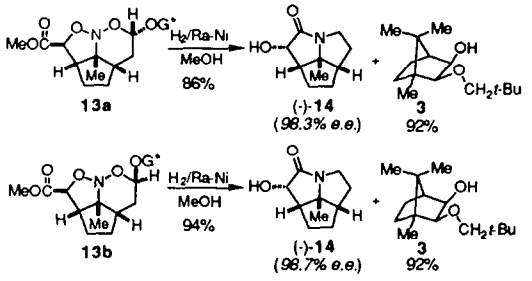
cycloadducts from **2** (**19a/19b**), ring C exists in a chair conformation[23] and analysis of the coupling pattern is simpler. In the major isomers, HC(5) resonates at significantly higher field and contains one large (10 Hz) and one small (2 Hz) coupling. These data are most consistent with an axial orientation, placing the OR group equatorial (α-anomer). With this in mind, it is possible to analyze the patterns for the cycloadducts **13** in terms of a single twist boat conformation which places the OR group of the α-anomer (**13a**) and the β-anomer (**13b**) in pseudoequatorial and pseudoaxial orientations, respectively. *Thus, for all tandem cycloadditions, the major isomer displays an α-oriented alkoxy group arising from an endo transition state for the [4+2]-cycloaddition.*

Finally, in large scale tandem cycloadditions, a third component (**13c**) was detected in trace quantities (<0.5%). The diagnostic ^{1}H NMR resonances (Table 2) suggest that it is also an exo isomer. The implications of these results are discussed below.

2. *Cleavage of Nitroso Acetals* **13a/13b**. To determine the extent of asymmetric induction in the cycloaddition and demonstrate the synthetic utility of the process, the separated isomers **13a** and **13b** were independently transformed to tricyclic lactam **14**, Scheme VI. Thus, hydrogenation at atmospheric pressure over Raney nickel afforded the levorotatory ($[\alpha]_D^{23}$ -34.4 ($CHCl_3$)) tricyclic lactam **14** in good yield along with an excellent recovery of the auxiliary alcohol, **3**. The product from the major cycloadduct (**13a**) was shown to be highly enantiomerically enriched (98.3% e.e.) by chiral HPLC analysis of the 3,5-dinitrophenyl carbamate (3,5-DNPC) derivative **15**.[24] The enantiomers of **15** are well-separated (α = 3.55) on a Pirkle L-Naphthylalanine column.

Remarkably, *the product from the minor cycloadduct (13b) was equally enantiomerically enriched* (98.7% e.e.). Moreover, from the elution order of the enantiomers, it was immediately obvious that the products belonged to the same configurational family. Thus, the separation of the anomers is not necessary to obtain highly enantiomerically enriched products.

Scheme VI

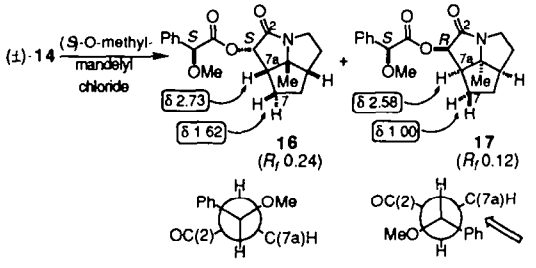


3. Determination of Configuration. To establish the absolute configuration of the lactam **14**, we made use of two empirical, but well founded techniques, chemical shift nonequivalence and chiral HPLC elution order. Recently, Trost[25a] has expanded the original methods of Mislow[25b] and Mosher[25c] to the use of O-methylmandelate esters for establishing absolute configuration of chiral alcohols. The (*S*)-O-methylmandelate esters of racemic **14** were prepared and the easily separated diastereomers fully characterized, Scheme VII. The more polar diastereomer **17** showed a significant upfield shift of the HC(7a) and HC(7) protons compared to the less polar diastereomer **16**. The conformational model for the O-methylmandelate esters is also shown in Scheme VII.[26] From the "extended Newman projections" it is seen that the shielding of HC(7a) and HC(7) by the phenyl ring (arrow, Scheme VII) is expected in the isomer with the (*R*)-configuration at C(1). Thus, the more polar diastereomer **17** is assigned the (1*R*)-configuration obviously deriving from (1*R*)-**14**.

Preparation of the (*S*)-O-methylmandelate derivative of (-)-**14** derived from **13a** gave the *less polar diastereomer* **16** by TLC and ^{1}H NMR comparison. Thus, the levorotatory tricyclic lactam produced from both cycloadducts bears the (1*S*,3*R*,5a*S*,7a*S*,7b*R*) configuration.

This assignment is corroborated by the chiral HPLC elution order. Pirkle has extensively developed the use of chiral HPLC with stationary phases derived from L-amino acids for the separation of alcohols, amines, amino acids, etc.[24b] From a large body of empirical data (supported by recent modeling studies),[24c,24d] it is seen that, in general, the (*S*)-enantiomer is more strongly retained. Indeed, the 3,5-DNPC of (-)-**14** from **13a** or **13b** corresponds to the later eluting isomer of **15**, again supporting the assignment of (-)-**14** as the (1*S*)-enantiomer.

Scheme VII



4. Other Chiral Vinyl Ethers. The extremely high selectivity obtained with vinyl ether **6** was very gratifying. Moreover, it was unlikely that the other chosen auxiliaries would be still more selective. Nonetheless, the vinyl ethers **7** and **10** were briefly examined. Using the optimized conditions developed for **6**, both **7** and **10** suffered extensive decomposition. In reactions run as cold as -100°C the only isolable products were recovered **1** and the alcohols **4** and **5**. Even using the more reactive substrate (*E*)-2-methyl-2-nitrostyrene, no cycloaddition products were detected. With a selective vinyl ether in hand, closer scrutiny of the problems with **7** and **10** was not of interest. However, other auxiliaries are actively being surveyed to provide access to both enantiomeric series using more readily available chiral alcohols.

C. TANDEM CYCLOADDITION WITH 2

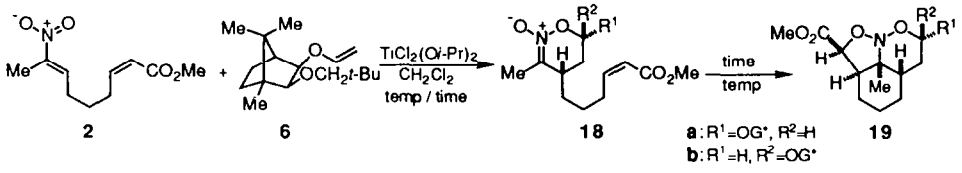
1. Optimization of Reaction Conditions. From the previous studies on cycloaddition of nitroalkene **2** with *n*-butyl vinyl ether it was known that the three atom tether changes the reaction course in two

important ways: 1) the [3+2]-cycloaddition is sufficiently slow that the intermediate nitronates **ii** are isolable and 2) the A/B ring fusion created in the [3+2]-cycloaddition is *trans*. This behavior was mirrored in the reactions with **6**. Orienting experiments, Table 3, used the optimized protocol developed for cycloaddition with **1**. Under these conditions, the nitronates could be obtained in good yield with a high selectivity for the α-anomer, **18a** (entry 1). Subsequent heating of the purified nitronate induced [3+2]-cycloaddition to provide tandem cycloadduct **19a** in good yield. To obtain the β-isomer for comparison studies, reaction conditions were adjusted as discussed for **1** above. Surprisingly, neither longer reaction times nor additional amounts of catalyst induced formation of a significant portion of the minor isomer, **18b** (entries 2 and 3). However, in preparative scale reactions (1-1.5 mmol, entries 4 and 5) the ratios changed significantly and without apparent cause.[27] Once again, trace amounts (2%) of a third isomer **18c** were detected and separately heated to effect [3+2]-cycloaddition. The thermal cycloaddition of the minor nitronate **18b** was examined and was found to proceed more rapidly than **18a** but not as cleanly (entry 5), the nitroso acetal **19b** being contaminated with another isomer. This observation is precedented in the behavior of the nitronates obtained from **2** with *n*-butyl vinyl ether.[11] In those studies as well, the β-anomer reacted in both lower yield and with lower selectivity than the α-anomer.

The structures of the nitronates **18** and nitroso acetals **19** are solidly based on the assignments made in the forgoing work.[11] The assignment of anomer configuration in the nitronate is difficult at best. Fortunately, as described above, the analysis of HC(5) in the nitroso acetals is straightforward owing to a chair conformation of the C ring. The diagnostic pattern (dd) for the α-anomeric configuration is also evident in the trace by-product **19c**, Table 2. It is interesting to note, in passing, the unusually small gauche coupling for $J_{5,6}$ in the α-anomer. This is most likely due to its rigidly-held antiperiplanar relationship to the C(5)-O(4) bond.[28]

2. Cleavage of Nitroso Acetals 19a and 19b. Following the precedent in the *n*-butyl vinyl ether cycloadducts, the hydrogenolyses of **19a** and **19b** were carried out at elevated pressures. Thus treatment of the major nitroso acetal **19a** with hydrogen over Raney nickel at 160 psi effected formation of the hydroxy ester **20** with concommitant release of **3**.

Table 3. Tandem Cycloaddition of **2** with **6**.



2 **6** **18** **19**

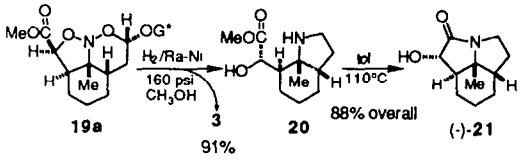
a: R^1=OG*, R^2=H
b: R^1=H, R^2=OG*

[4+2]-cycloaddition[a]							[3+2]-cycloaddition[b]			
entry	**6**, equiv	Lewis acid	temp, °C	time, h	ds[c]	yield,%[d]	educt[e]	temp, °C	time, h	yield,%[f]
1	1.3	2.4	-78	2	24/1	91	**18a**	60	10.5	90
2	1.3	2.4	-78	22	32/1	71				
3	1.3	3.0	-78	8.5	15/1	76				
4	1.2	2.6	-78	15	1.5/1	75	**18a**	60	11	53
							18b	60	7.5	11
5	1.2	2.6	-78	14.5	5.8/1	87[g]	**18a**	40	24	86
							18b	40	6	78[h]

[a]All reactions in CH_2Cl_2. [b]All reactions in toluene. [c]Ratio of isolated **18a/18b**. [d]Combined yield of isolated **18**. [e]Purified nitronate. [f]Yield of isolated **19**. [g]Trace of **18c** (2.2%) detected. [h]Contaminated with *ca.* 10% of another isomer.

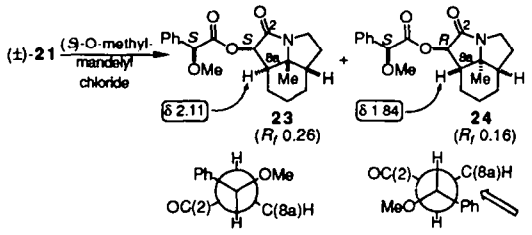
This mixture was not separated, but directly heated in toluene at reflux to afford the tricyclic lactam **21** along with the chiral alcohol **3** in very good yields, Scheme VIII. Unfortunately, treatment of the minor nitroso acetal **19b** under similar conditions failed to produce any of the desired product. Capricious hydrogenolysis reactions were noted previously in this series, but ultimately both anomers of the C(5) *n*-butoxy series could be cleaved. As the separation and individual treatment of the anomers **13a/13b** was shown above to be unnecessary, this problem was left unsolved.

Scheme VIII



3. Determination of Configuration. The tricyclic lactam **21** obtained from **19a** was levorotatory ($[\alpha]_D^{23}$ -113.4 ($CHCl_3$)) suggesting a configurational homology with (-)-(1*S*)-**14**. The enantiomeric purity and absolute configuration of (-)-**21** was established as described above for (-)-**14**. Thus, the 3,5-DNPC derivative of racemic **21** ((±)-**22**) was prepared and was easily resolved by chiral HPLC analysis ($\alpha = 4.01$). *The 3,5-DNPC derivative of (-)-21 showed an extremely high enantiomeric enrichment (99.0% e.e.).* As was the case for (-)-**14**, this material corresponded to the more retained isomer of **22** supporting the correlation by optical rotation, namely that (-)-**21** bears the (1*S*)-configuration. This assignment was confirmed by the preparation and analysis of the (*S*)-O-methylmandelate esters of racemic- and (-)-**21** as described above, Scheme IX. Although the two diastereomers **23** and **24** could be easily separated, the diagnostic resonances for HC(8a) and HC(8) were obfuscated in multiproton multiplets. However, at 500 MHz, the HC(8a) resonances could be located with the aid of homonuclear decoupling. Once again, the more polar diastereomer **24** displayed a significant upfield shift of HC(8a) compared to the less polar diastereomer **23**.

Scheme IX



By the established conformational model, the assignment follows analogously leading to the conclusion that **23** and **24** possess the (1*S*)- and (1*R*)-configurations, respectively. The (*S*)-O-methylmandelate derivative of (-)-**21** derived from **19a** corresponded to **23** by chromatographic and spectroscopic comparison. Accordingly, the levorotatory tricyclic lactam **21** is assigned the (1*S*,3*R*,5a*S*,8a*R*,8b*R*) configuration, thus, indeed belonging to the same configurational family as (-)-**14**.

DISCUSSION

There are many different features of this reaction for which an in-depth analysis would provide fascinating insights. Since the focus of this report has been the asymmetric induction with chiral dienophiles, the discussion below is limited to those mechanistic and stereochemical issues relevant to the [4+2]-cycloaddition. The details of structure, reactivity and stereoselectivity which attend the [3+2]-cycloaddition and subsequent chemical transformations will be discussed in forthcoming articles.

A. MECHANISM

The central mechanistic questions in the Lewis acid-induced [4+2]-cycloaddition are: 1) is the reaction concerted or stepwise and 2) are the products configurationally stable? Ultimately, from a stereochemical point of view, these questions are moot as the configuration of the entire molecule is established in the first bond forming event (**iii**, Scheme II). If this step is irreversible, then the timing and topicity of the second bond formation to create the nitronate ring and the anomeric stereocenter are irrelevant. These features are of interest only to explain the origin of selectivity by reducing the

stereochemical information to a reasonable transition structure.

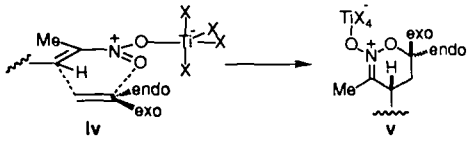
The results described in this report do not allow an unambiguous conclusion to be drawn concerning reversibility and concertedness. However, in these laboratories, parallel studies of **1** with *cis*- and *trans*-1-propenyl ethyl ether can be interpreted as proceeding by an irreversible [4+2]-cycloaddition either concerted or stepwise. Further, the methyl group in these products allowed a clear demonstration of the configurational lability of the anomeric center during the reaction. Thus, by analogy we conclude that **6** also reacts irreversibly. However, the kinetic composition of the α- and β-anomers is uncertain. The observed variation in anomer ratio under different reaction conditions clearly suggests that they are interconvertible. Moreover, the fact that both **13a** and **13b** lead to the same enantiomer of **14** with the same level of enantiomeric excess strongly supports the contention that only one isomer is produced kinetically. In this scenario, the stereochemical outcome is completely set in **iii** (to **13a**) or **18a**, the presumed products of kinetic control, and subsequent anomerization is inconsequential. Alternatively, it is possible, though unlikely, that both **13a** and **13b** (**18a** and **18b**) are formed kinetically in the same topological sense. In the following discussion of stereochemistry, both scenarios are presented and evaluated.

B. STEREOCHEMISTRY

To fully understand the origin of the extreme diastereoselectivities observed, the stereochemical controlling features of the reaction must be clarified. Basically, the enanantiotopic faces of the nitroalkene-titanium complex are distinguished with high sensitivity by the chiral reagent due to large energy differences in the possible diastereomeric transition structures. There are three critical control elements that conspire to distinguish these ensembles: 1) the orientation (exo or endo) of the vinyl ether with respect to the heterodiene, 2) the accessibility of the vinyl ether diastereofaces and 3) the conformation (*s-cis* or *s-trans*) of the vinyl ether moiety. These issues are individually discussed in detail below.

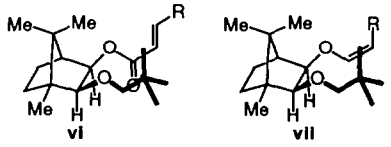
1. Endo/Exo Orientation. For reasons discussed above, it is believed that the α-anomers **iii** (to **13a**) and **18a** are the products of kinetic control. Scheme X shows clearly that these isomers must arise from an endo orientation of the alkoxy group in the transition structure **iv**. The preferred endo orientation of a heteroatom in inverse electron demand Diels-Alder reactions is documented for vinyl ethers,[14c,29a-c] vinyl sulfides[29b] and enamines.[29d] Indeed, we have also observed this behavior in cycloadditions of nitroso alkenes with vinyl ethers[30a] and vinyl sulfides.[30b] The origin of the effect is unclear, but secondary orbital interactions (Alder endo rule)[31a] have been invoked.[30b] The endo orientation of a seemingly bulky isobornyl group is noteworthy.

Scheme X



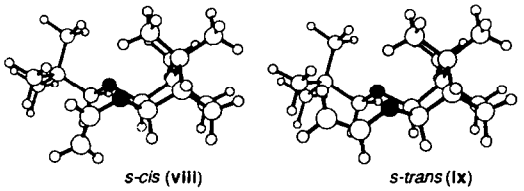
2. Vinyl Ether Diastereoface Accessibility. As part of a general program on the evaluation of camphor derivatives as chiral auxiliaries, Oppolzer surveyed a series of 2,3-bornanediols.[1d] The 3-neopentyl ether was found to give high selectivities in a variety of reactions involving C(2) acylated functions. Thus, Diels-Alder reactions of the acrylate, fumarate, butadienoate and N-sulfinylcarbamate proceeded with >99% d.e. Furthermore, cuprate additions to the 2-crotonate as well as ene reactions on the 2-glyoxylate were also selective (80% d.e.). The configuration of the major products and the high selectivities obtained in these reactions can be understood in terms of the reactive conformation **vi** shown in Chart II. By taking advantage of the intrinsic conformational preferences of unsaturated esters[32], the 3-neopentyloxy group provides effective shielding of the "inner" π-face. In a more analogous study, Greene showed that the 2-[(Z)-1-propenyl] ether **vii** also reacted selectively (80% d.e.) on the *si* (outer) face in a ketene [2+2]-cycloaddition. Thus, while the principal reaction trajectory is "outside" due to the neopentyloxy group, the reaction topicity is dependent on which face is exposed, i.e. the conformation of the vinyl ether.

Chart II



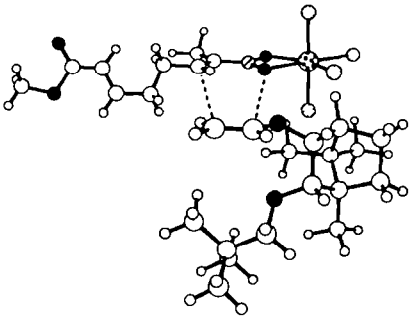
3. Conformation of the Vinyl Ether. The ground state conformation of vinyl ethers has been the subject of intense scrutiny.[33] There is now general agreement between experimental and computational studies that unsubstituted vinyl ethers prefer a *cisoid*-staggered conformation. A second minimum, 1.2 Kcal/mol higher in energy and separated by a small (4.5 Kcal/mol) barrier is the *transoid*-staggered form. This picture is well reproduced in the minimized (MM2) ground state structures of **6** showing the *cisoid* form (**viii**) more stable than the *transoid* form (**ix**) by 1.4 Kcal/mol, Chart III. In this projection, the shielding effect of the neopentyloxy group is easily seen. Thus, in this enantiomer of the auxiliary, the accessible faces are *re* in the *cisoid* (**viii**) and *si* in the *transoid* (**ix**) conformers. While there are interesting differences in the structural details of these two conformers, the energy difference between them is too small to warrant extrapolation. Clearly, any small steric or electronic preference in **viii** and **ix** can be overcome when challenged with the demands of the transition structures leading to products.

Chart III



4. Transition Structure Analysis. To formulate a transition structure for the [4+2]-cycloaddition now involves integration of the features discussed above with the critical stereochemical attributes of the products. In principle, there are 2^3 or eight possible permutations leading to four possible products. Since only two products are formed, four permutations are *a priori* removed. Thus, for each of the two observed products, there are two possible transition structures of which only one is reasonable. From the configurational assignments of (-)-**14** and (-)-**21**, it is unambiguously established that the *re*-face of the nitroalkenes **1** and **2** is preferentially attacked ((5a*S*)-configuration produced). In the first scenario, the endo isomer is formed exclusively. Thus, the relative topicity of the reaction requires the *si*-face of the vinyl ether. This can be accommodated by the *transoid* conformer **ix** by external attack as shown in Chart IV.[34] The only other alternative which satisfies these conditions requires "inside" attack on the *cisoid* conformer **viii**. This is easily excluded. In the second scenario wherein both cycloadducts are kinetically derived, the topicity for exo product formation requires the *re*-face of the vinyl ether. This is best accommodated by external attack on the *cisoid* conformer **viii**. The alternative inside attack on **ix** is clearly not feasible.

Chart IV



An interesting question arises from this transition structure analysis: why does **6** prefer to react via the (slightly) less stable conformation **ix**? The answer may well be found in the strong endo preference for this class of reactions. In order for **6** to simultaneously satisfy both preferences, i.e reaction via an endo transition structure and in conformation **viii** (leading to the opposite configurational family)[35], the nitroalkene is unavoidably presented with the bornane skeleton in a fashion not encountered in reaction with **ix**. Thus, the magnitude of the endo preference for **6** in the transition structure and the facility with which this orientation can be achieved in reaction with **ix**, easily outweigh the small ground state preference for **viii**.[36]

In summary, the tandem [4+2]/[3+2]-cycloaddition of nitroalkenes has been shown to proceed with extremely high diastereoselectivity using a chiral vinyl ether as the triggering dienophile. The reactions proceed in good yield with a minimal excess of the vinyl ether under mild conditions. The nitroso acetals resulting from tandem cycloaddition can be easily transformed by hydrogenation into α-hydroxy lactams in good yield and high enantiomeric excess (>98% e.e.) with excellent recovery of the auxiliary alcohol. A stereochemical model based on a high endo preference for the vinyl ether explains the magnitude of the selectivities observed. Current efforts focus on: 1) substituted vinyl ether dienophiles, 2) the development of simpler, selective auxiliaries and 3) chiral Lewis acid catalysts.

EXPERIMENTAL

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz ^{1}H, 75.5 MHz ^{13}C), or a General Electric GN-500 (500 MHz ^{1}H), spectrometer with chloroform (δ 7.26) as an internal standard in $CDCl_3$ solutions unless otherwise stated. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) or br (broadened). Coupling constants, *J*, are reported in Hz. Assignments of individual resonances are supported by APT and DEPT spectra in most instances. Infrared spectra were obtained on a Perkin-Elmer 1320, or Nicolet 7199c FT IR spectrometer as a neat liquid, chloroform or carbon tetrachloride solution or KBr pellet. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 34-66%), w (weak, 0-33%). Mass spectra (EI) were obtained on a Finnigan MAT CH-5 spectrometer or a Finnigan MAT 311A with an ionization voltage of 10 or 70 eV. Data are recorded in the form *m/z* (intensity relative to base=100). High-resolution (EI) mass spectra were obtained on a Finnnigan MAT 731 spectrometer. High-resolution (FAB) mass spectra were obtained on a VG-ZAB-2F spectrometer.

Melting points were obtained on a Thomas Hoover capillary melting point apparatus in evacuated capillary tubes and are corrected. Bulb-to-bulb distillations were done on a Buchi GKR-50 Kugelrohr; boiling points (bp) refer to air bath temperatures and are uncorrected. Analytical TLC was performed on 0.25 mm silica gel plates (Merck) with QF-254 indicator. Visualization was accomplished with UV light, phosphomolybdic acid, iodine, sulfuric acid/methanol, vanillin and/or 2,4-DNP solution. Column chromatography was performed on 32-63 μ silica gel (Woelm) with distilled technical grade solvents. Reaction solvents were distilled under a N_2 atmosphere from the following agents: tetrahydrofuran (THF), diethyl ether from sodium/benzophenone, hexane, methylene chloride, benzene and toluene from calcium hydride, and acetonitrile from phosphorus pentoxide, and then from calcium hydride. All reactions were performed in oven (140°C) or flame dried glassware under an inert atmosphere of dry N_2. Analytical high pressure liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 Liquid Chromatograph and a Perkin Elmer LC-75 Spectrophotometric Detector using a Pirkle Covalent L-Naphthylalanine column (250 x 4.5 mm, 5μ (Regis)). Retention times (t_R) and integrated ratios were obtained from a Hewlett Packard 3390A integrator. Solvents for HPLC were distilled in glass or spectro grade and filtered immediately prior to use. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-2-ethynyloxy-4,7,7-trimethylbicyclo[2.2.1]-heptane (8). To a suspension of oil-free potassium hydride (450 mg, 11.25 mmol, 3.0 equiv) in THF (7.5 mL) was added dropwise with stirring a solution of 900 mg (3.75 mmol) of (1*S*,2*R*,3*S*,4*R*)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**3**) in THF (7.5 mL). The mixture was stirred at room temperature for 4 h, cooled to -78°C, treated with a solution of trichloroethylene (492 mg, 3.75 mmol) in THF (5 mL) and was allowed to warm to room temperature. After being stirred for 1 h, the dark brown mixture was treated with *n*-butyllithium (7.1 mL, 1.58 M in hexane, 11.25 mmol, 3.0 equiv) dropwise at -70°C. After 0.5 h at -70°C, the mixture was warmed to 0°C and was poured into a cold sat. aq. NH_4Cl solution. The mixture was extracted with pentane (3 x 100 mL) and washed with brine. The organic extracts were dried (Na_2SO_4), filtered and concentrated to give a brown residue. The crude product was purified by column chromatography on neutral alumina (pentane) to give 898 mg (90%) of **8** as a colorless oil. Data for **8**: bp 58-60°C (0.1 Torr); ^{1}H NMR (300 MHz) 4.19 (d, *J* = 6.4, 1 H, HC(2)), 3.27 (d, *J* = 6.4, 1 H, HC(3)), 3.39, 2.95 (ABq, *J* = 7.9, 2 H, $H_2C(1')$), 2.16 (d, *J* = 5.1, 1

H, HC(1)), 1.80-1.68 (m,1 H), 1.53 (s, 1 H, HC(2")), 1.50-1.43 (m, 1 H), 1.11(s, 3 H, CH_3), 1.03-0.91 (m, 2 H), 0.91 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.79 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 92.90 (C(2)), 91.60 (C(1")), 87.42 (C(3)), 83.01 (C(1')), 49.87 (C), 48.76 (C(1)), 46.58 (C), 33.26 (CH_2), 32.45 (C), 26.75 (CH_3), 26.38 (C(2")), 23.26 (CH_2), 20.81(CH_3), 20.31 (CH_3), 11.30 (CH_3); IR (neat) 3331 (m), 2955 (s), 2150 (s), 1475 (m), 1458 (m), 1393 (w), 1362 (m), 1289 (w), 1146 (s), 1117 (s), 1086 (m), 1061 (m), 1017 (w); MS (FAB) 265 (M+H, 0.59), 241 (13), 223 (13), 179 (31), 154 (14), 153 (100), 123 (14), 119 (29), 109 (33), 107 (11), 103 (23); high resolution MS (FAB) calcd for $C_{17}H_{29}O_2$ (M+H)) 265.21676, found 265.21700; TLC R_f 0.29 (hexane); Anal. Calcd for $C_{17}H_{29}O_2$ (265.217): C, 77.22; H, 10.67. Found: C, 77.20; H, 10.64.

(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-2-ethenyloxy-4,7,7-trimethylbicyclo[2.2.1]-heptane (6). A solution of the acetylenic ether **8** (1.0 g, 3.78 mmol), quinoline (490 μL, 4.16 mmol) in hexane (10 mL) was added to a suspension of preactivated 5% palladium on barium sulfate (6 mg). The system was charged with hydrogen and the reaction mixture was stirred at atmospheric pressure and room temperature until the complete consumption of the starting material. The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (neutral alumina, pentane) to give 921 mg (92%) of **6** as a clear, colorless oil. Data for **6** are reported for a distilled sample: bp 50°C (2.4 x 10^{-4} Torr); ^1H NMR (300 MHz) 6.39 (dd, *J* = 14.3, 6.8, 1 H, HC(1")), 4.11 (dd, *J* = 14.5, 1.1, 1 H, HC(2")), 3.94 (dd, *J* = 6.6, 1.1, 1 H, HC(2")), 3.87 (d, *J* = 6.6, 1 H, HC(2)), 3.24, 2.92 (ABq, *J* = 7.8, 2 H, $H_2C(1')$), 3.22 (d, *J* = 6.5, 1 H, HC(3)), 1.83 (d, *J* = 4.8, 1 H, HC(1)), 1.73-1.62 (m, 1 H), 1.52-1.41 (m, 1 H), 1.12 (s, 3 H, CH_3), 1.04-0.95 (m, 2 H), 0.90 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 151.91 (C(1")), 87.98 (C(2)), 86.64 (C(2")), 83.39 (C(3)), 82.69 (C(1')), 49.55 (C), 49.09 (C(1)), 46.68 (C), 33.35 (CH_2)), 32.48 (C), 26.89 (CH_3), 23.95 (CH_2), 21.07 (CH_3), 20.61 (CH_3), 11.54 (CH_3); IR (neat) 2953 (s), 1633 (m), 1607 (m), 1478 (m), 1460 (m), 1371 (m), 1362 (m), 1202 (s), 1119 (s), 1098 (m), 1078 (m), 1017 (w), 964 (m), 810 (w); MS (FAB) 267 (M+H, 13), 241 (22), 223 (15), 181 (34), 163 (18), 155 (58), 153 (100), 152 (29), 137 (15), 135 (50), 123 (19), 121 (19), 119 (100), 115 (58), 109 (33), 103 (60); high resolution MS (FAB) calcd for $C_{17}H_{31}O_2$ (M+H)) 267.2320, found 267.2324; TLC R_f 0.39 (hexane); Anal. Calcd for ($C_{17}H_{30}O_2$) C, 76.64; H, 11.5; found C, 76.97; H, 11.63.

Methyl (1*S*,3*R*,5*S*,6a*S*,8a*S*,8b*R*)-5-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-8b-methyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isoxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (13a) and Methyl (1*S*,3*R*,5*R*,6a*S*,8a*S*,8b*R*)-5-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-8b-methyl-6a,7,8,8a-tetrahydrocyclopenta[1,2,3-*hj*]isooxazolo[2,3-*b*][1,2]oxazine-1-carboxylate (13b). To a magnetically-stirred, cold (-78°C) solution of **1** (199 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added a freshly prepared solution of dichlorotitanium diisopropoxide (2.4 mmol, 2.4 equiv) in CH_2Cl_2 (2 mL). After stirring for 10 min, a solution of **6** (317 mg, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. The resulting pale yellow solution was stirred at -78°C for 22.5 h and then quenched with a 1N solution of NaOH in methanol (4.8 mL). The cold bath was removed and the mixture was allowed to warm to room temperature. The mixture was poured into CH_2Cl_2 (75 mL), washed with water (3 x 50 mL) and the aqueous solutions were back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$/$NaHCO_3$, 1/1) and concentrated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc, 20/1) to afford 308 mg of (66%) **13a** and 75 mg (16%) of **13b** as colorless amorphous solids along with 16 mg (8%) of recovered **1**. Data for **13a**: ^1H NMR (300 MHz) 5.10 (dd, *J* = 6.3, 2.6, 1 H, HC(5)), 4.88 (d, *J* = 8.2, 1 H, HC(1)), 3.80 (s, 3 H, $H_3C(11)$), 3.76 (d, *J* = 6.7, 1 H, HC(2')), 3.18, 2.94 (ABq, *J* = 7.9, 2 H, $H_2C(1")$), 3.15 (d, *J* = 6.7, 1 H, HC(3')), 2.72 (td, *J* = 7.7, 3.2, 1 H, HC(8a)), 2.23-2.15 (m, 1 H), 2.00-1.30 (m, 11 H), 1.30 (s, 3 H, $H_3C(9)$), 1.09 (s, 3 H, CH_3), 0.90 (s, 9 H, 3 x $H_3C(3")$), 0.86 (s, 3 H, CH_3), 0.74 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 169.97 (C(10)), 100.70 (C(5)), 88.06 (CH), 86.84 (CH), 84.99 (CH), 83.32 (C(8b)), 82.53 (C(1")), 57.13 (C(8a)), 52.03 (C(2")), 51.41 (CH), 49.25 (C), 46.27 (C), 43.37 (C(6a)), 33.63 (CH_2), 33.45 (CH_2), 32.24 (C), 28.78 (CH_2), 28.10 (CH_2), 26.79 (CH_3), 24.24 (C(9)), 23.86 (CH_2), 20.83 (CH_3), 20.78 (CH_3), 11.45 (CH_3); IR (CCl_4) 2955 (s), 2872 (m), 1744 (m), 1478 (w), 1439 (m), 1362 (w), 1266 (m), 1202 (w), 1181 (w), 1148 (m), 1100 (m), 1051 (w), 1020 (w), 837 (w); MS (FAB) 466 (M+H, 25), 244 (69), 228 (55), 226 (46), 224 (16), 212 (11), 210 (14), 198 (13), 155 (32), 153 (100), 135 (33), 123 (22), 119 (66), 109 (36), 107 (17), 103 (35); high resolution MS calcd for $C_{26}H_{44}NO_6$ (M+H) 466.3169, found 466.3165; TLC R_f 0.56 (hexane/EtOAc 5/1). Data for **13b**: ^1H NMR (300 MHz) 5.12 (t, *J* = 7.3, 1 H, HC(5)), 4.85 (d, *J* = 8.3, 1 H, HC(1)), 4.02 (d, *J* = 6.7, 1 H, HC(2')), 3.78 (s, 3 H, $H_3C(11)$), 3.70, 2.78 (ABq, *J* = 7.9, 2 H, $H_2C(1")$),

3.21 (d, J = 6.7, 1 H, HC(3')), 2.72 (m, 1 H, HC(8a)), 2.01 (dd, J = 14.5, 7.3, 1 H, HC(6)), 1.94-1.79 (m, 4 H), 1.73 (ddd, J = 14.3, 7.2, 2.6, 1 H, HC(6)), 1.68-1.19 (m, 5 H), 1.32 (s, 3 H, H_3C(9)), 1.10 (s, 3 H, CH_3), 1.07-0.92 (m, 1 H), 0.89 (s, 9 H, 3 x H_3C(3")), 0.85 (s, 3 H, CH_3), 0.75 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 170.31 (C=O), 96.01 (C(5)), 87.37 (CH), 87.08 (CH), 85.18 (C(8b)), 81.57 (C(1")), 79.61 (CH), 56.99 (C(8a)), 52.37 (C(11)), 49.28 (C), 47.64 (CH), 46.69 (C), 43.44 (C(6a)), 33.84 (CH_2), 32.32 (C), 31.70 (CH_2), 28.40 (C(8)), 27.01 (CH_3), 26.85 (C(7)), 23.86 (CH_2), 23.83 (C(9)), 21.28 (CH_3), 20.86 (CH_3), 11.52 (CH_3); IR (CCl_4) 2953 (s), 2874 (m), 1744 (m), 1478 (w), 1439 (w), 1360 (m), 1285 (w), 1202 (w), 1181 (w), 1150 (m), 1134 (m), 1115 (m), 1092 (m), 1075 (m), 1036 (m), 1005 (m); MS (FAB) 466 (M+H, 12), 244 (20), 228 (32), 227 (20), 226 (100), 223 (18), 210 (17), 198 (35), 169 (22), 166 (20), 154 (14), 153 (88), 138 (11), 137 (10), 135 (33), 125 (13), 123 (35), 121 (12), 119 (23), 109 (39), 107 (22); high resolution MS calcd for $C_{26}H_{44}NO_6$ (M+H) 466.3169, found 466.3165; TLC R_f 0.63 (EtOAc/hexane 5/1).

Hydrogenolysis of 13a. (1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1Hydroxy-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta-[1,2,3-*gi*]pyrrolidino[1,2-*a*]pyrrolidine (1*S*)-(14). To a solution of **13a** (275 mg, 0.59 mmol) in methanol (15 mL) was added a catalytic amount of Raney nickel. The suspension was stirred under H_2 (1 atm) at room temperature for 36 h, filtered through a celite pad, and concentrated. The residue was purified by column chromatography (silica gel; hexane, hexane/EtOAc, 10/1-1/1) to afford 92 mg (86%) of (1*S*)-**14** as a white solid and 130 mg (92%) of recovered **3**. Data for (1*S*)-**14**: ^1H NMR (300 MHz) 4.68 (d, J = 7.2, 1 H, HC(1)), 3.89 (ddd, J = 12.0, 8.5, 3.6, 1 H, HC(4)), 3.32 (br, 1 H, HOC(1)), 2.93 (dt, J = 11.8, 8.0, 1 H, HC(4)), 2.62 (q, J = 7.4, 1 H, HC(7a)), 2.25 (m, 1 H), 2.11 (m, 1 H), 1.76 (m, 3 H), 1.47 (m, 1 H), 1.31 (s, 3 H, H_3C(8)), 1.26 (m, 1 H); ^{13}C NMR (75.5 MHz) 176.62 C(2)), 75.55 (C(7b)), 72.81 (C(1)), 51.08 (C(7a)), 49.20 (C(5a)), 42.07 (C(4)), 31.47 (C(5)), 30.96 (C(7)), 24.85 (C(6)), 22.82 (C(8)); IR (CCl_4) 3386 (w), 2963 (m), 2870 (w), 1707 (s), 1404 (m), 1377 (w), 1363 (w), 1335 (m), 1225 (w), 1202 (w), 1150 (m), 1086 (w); MS (70 eV) 182 (M^+ + 1, 11), 181 (M^+, 93), 166 (100), 162 (13), 138 (63), 123 (13), 110 (20), 107 (34), 98 (18), 96 (36), 93 (27), 83 (51), 79 (23), 67 (35), 57 (47), 55 (64), 41 (68), 39 (39); TLC R_f 0.13 (hexane/EtOAc, 1/1); ($[\alpha]_D^{23}$ -34.4 (1.0, $CHCl_3$))

Hydrogenolysis of 13b. (1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1-Hydroxy-7b-methyl-2-oxo-5a,6,7,7a,-tetrahydrocyclopenta-[1,2,3-gi]pyrrolidino[1,2-a]pyrrolidine (1*S*)-14. The procedure described above provided 47.5 mg (94%) of (1*S*)-**14** along with 62 mg (92%) of recovered **3**. Data for (1*S*)-**14**: ^1H NMR (300 MHz) 4.68 (d, J = 7.3, 1 H, HC(1)), 3.90 (ddd, J = 12.0, 8.6, 3.6, 1 H, HC(4)), 2.94 (dt, J = 12.0, 8.1, 1 H HC(4)), 2.80 (br, 1 H, HOC(1)), 2.63 (q, J = 7.4, 1 H, HC(7a)), 2.26 (m, 1 H), 2.11 (m, 1 H), 1.73 (m, 3 H), 1.48 (m, 1 H), 1.32 (s, 3 H, H_3C(8)), 1.26 (m, 1 H); ^{13}C NMR (75.5 MHz) 176.37 (C(2)), 75.81 (C(7b)), 72.93 (C(1)), 51.24 (C(7a)), 49.30 (C(5a)), 42.24 (C(4)), 31.56 (C(5)), 31.15 (C(7)), 24.90 (C(6)), 23.00 (C(8)); IR (CCl_4) 3359 (br, w), 2961 (m), 2870 (m), 1707 (s), 1450 (w), 1404 (m), 1377 (w), 1363 (w), 1334 (m), 1296 (w), 1225 (w), 1199 (w), 1149 (m), 1086 (w); MS (70 eV) 182 (M^+ + 1, 11), 181 (M^+, 90), 166 (100), 162 (14), 138 (61), 123 (13), 108 (25), 107 (34), 96 (37), 93 (27), 82 (50), 77 (16), 67 (35), 57 (48), 55 (65), 41 (60); TLC R_f 0.14 (hexane/EtOAc, 1/1).

rac-(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1-[N-(3,5-dinitrophenyl)carbamoxy]-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta[1,2,3-gi]pyrrolidino[1,2-a]pyrrolidine (±)-(15). HPLC Analysis of (±)-14. A solution of 3,5-dinitrobenzoylazide (13 mg, 0.055 mmol, 1.1 equiv) in toluene (5 mL) was heated to reflux for 10 min, and a solution of (±)-**14** (9 mg, 0.05 mmol) in toluene (1 mL) was added. The mixture was heated to reflux for 10 min, cooled to room temperature and concentrated. The white solid was recrystallized using EtOAc to give 15 mg (72%) of (±)-(**15**). Data for (±)-**15**: ^1H NMR (300 MHz) 9.90 (s, br, 1 H, NH), 8.63 (d, J = 1.8, 1 H, HC(5')), 8.57 (d, J = 1.8, 2 H, HC(3')), 5.93 (d, J = 7.0, 1 H, HC(1)), 3.96 (ddd, J = 12.1, 8.4, 3.7, 1 H, HC(4)), 3.07 (dt, J = 12.1, 8.1, 1 H, HC(4)), 2.82 (q, J = 7.2, 1 H, HC(7a)), 2.39 (m, 1 H), 2.24 (dtd, J = 12.3, 8.2, 4.0, 1 H, HC(5a)), 1.91-1.65 (m, 2 H), 1.58-1.47 (m, 1 H), 1.44 (s, 3 H, H_3C(8)), 1.32-1.25 (m, 1 H); ^{13}C NMR (75.5 MHz) 171.97 (C(2)), 152.46 (C(1')), 148.71 (C(4')), 141.10 (C(2')), 118.16 (C(5')), 112.60 (C(3')), 76.15 (C(7b)), 75.15 (C(1)), 49.55 (C(7a)), 49.34 (C(5a)), 42.46 (C(4)), 31.69 (C(5)), 31.08 (C(7)), 25.85 (C(6)), 22.81 (C(8)); IR ($CDCl_3$) 2930 (m), 1742 (m), 1692 (m), 1547 (s), 1426 (m), 1347 (m), 1246 (m), 1223 (m), 1138 (w); TLC R_f 0.28 (hexane/EtOAc, 1/1); HPLC (Pirkle; hexane/EtOAc, 7/3, 1.5 mL/min) t_R (1*R*)-**15**, 7.37 min (50.0%), t_R (1*S*)-**15**, 23.54 min (50.0%).

HPLC Analysis of (-)-14 from 13a. A solution of 3,5-dinitrobenzoylazide (9 mg, 0.036 mmol, 1.1 equiv) in toluene (5 mL) was heated to reflux for 10 min, and a solution of (-)-**14** from **13a** (6 mg, 0.033 mmol) in toluene (1 mL) was added. The mixture was heated to reflux for 10 min, cooled to room temperature and concentrated. The off-white solid was purified by column chromatography (silica gel; hexane/EtOAc, 3/1-1/1) to give 11 mg (85%) of (1*S*)-**15** as a white solid. Data for (1*S*)-**15**: ^{1}H NMR ($CDCl_3$) 10.23 (s, br, 1 H, HN), 8.61 (d, J = 1.9, 1 H, HC(5')), 8.56 (d, J = 1.8, 2 H, HC(3')), 5.95 (d, J = 7.2, 1 H, HC(1), 3.95 (ddd, J = 12.2, 8.4, 3.7, 1 H, HC(4)), 3.09 (dt, J = 12.1, 8.0 1 H, HC(4)), 2.81 (q, J = 7.2, 1 H, HC(7a)), 2.39 (m, 1 H), 2.24 (dtd, J = 12.4, 8.3, 4.1, 1 H, HC(5a)), 1.91-1.79 (m, 2 H), 1.77-1.65 (m, 1 H), 1.57-1.48 (m, 1 H), 1.45 (s, 3 H, H_3C(8)), 1.32-1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) 172.15 (C(2)), 152.52 (C(1')), 148.66 (C(4')), 141.18 (C(2')), 118.12 (C(5')), 112.52 (C(3')), 76.16 (C(7b)), 74.92 (C(1)), 49.52 (C(7a)), 49.30 (C(5a)), 42.46 (C(4)), 31.69 (C(5)), 31.04 (C(7)), 25.85 (C(6)), 22.74 (C(8)); IR ($CDCl_3$) 3110 (w), 2965 (w), 2253 (w), 1742 (m), 1694 (s), 1547 (s), 1426 (m), 1347 (s), 1246 (m), 1223 (m), 1138 (m); TLC R_f 0.28 (hexane/EtOAc, 1/1); HPLC (Pirkle; hexane/EtOAc, 7/3; 1.5 mL/min) t_R (1*R*)-**15**, 7.48 min (0.87%); t_R (1*S*)-**15**, 23.18 min (99.13%).

HPLC Analysis of (-)-14 from 13b. A solution of 3,5-dinitrobenzoylazide (9 mg, 0.036 mmol, 1.1 equiv) in toluene (5 mL) was heated to reflux for 10 min, and a solution of (-)-**14** from **13b** (6 mg, 0.033 mmol) in toluene (1 mL) was added. The mixture was heated to reflux for 10 min, cooled to room temperature and concentrated. The off-white solid was purified by column chromatography (silica gel; hexane/EtOAc, 3/1-1/1) to give 10 mg (77%) of (1*S*)-**15** as a white solid. Data for (1*S*)-**15**: ^{1}H NMR ($CDCl_3$) 10.28 (s, br, 1 H, HN), 8.61 (d, J = 1.7, 1 H, HC(5')), 8.55 (d, J = 1.9, 2 H, HC(3')), 5.95 (d, J = 7.2, 1 H, HC(1)), 3.95 (ddd, J = 12.1, 8.4, 3.7, 1 H, HC(4)), 3.08 (dt, J = 12.1, 8.0, 1 H, HC(4)), 2.81 (q, J = 7.2, 1 H, HC(7a)), 2.40 (m, 1 H), 2.24 (dtd, J = 12.4, 8.2, 4.0, 1 H, HC(5a)), 1.91-1.77 (m, 2 H), 1.74-1.64 (m, 1 H), 1.54-1.47 (m, 1 H), 1.45 (s, 3 H, H_3C(8)), 1.32-1.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) 172.18 (C(2)), 152.54 (C(9)), 148.67 (C(4')), 141.21 (C(2')), 118.12 (C(5')), 112.52 (C(3')), 76.18 (C(7b)), 74.90 (C(1)), 49.53 (C(7a)), 49.32 (C(5a)), 42.47 (C(4)), 31.70 (C(5)), 31.05 (C(7)), 25.86 (C(6)), 22.75 (C(8)); IR ($CDCl_3$) 2963 (w), 1692 (m), 1547 (s), 1426 (w), 1347 (m), 1246 (m), 1223 (m), 1138 (w); TLC R_f 0.28 (hexane/EtOAc, 1/1); HPLC (Pirkle; hexane/EtOAc, 7/3; 1.5 mL/min) t_R (1*R*)-**15**, 7.43 min (0.66%); t_R (1*S*)-**15**, 22.58 min (99.34%).

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1-[(*S*)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta[1,2,3-*gi*]pyrrolidino[1,2-*a*]pyrrolidine (16) and (1*R*,3*S*,5a*R*,7a*R*,7b*S*)-1-[(*S*)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta[1,2,3-*gi*]pyrrolidino[1,2-*a*]pyrrolidine (17). To a cold (0°C) solution of DMF (62 mg, 0.84 mmol, 1.5 equiv) in acetonitrile (2 mL) was slowly added oxalyl chloride (71.5 mg, 0.56 mmol, 1.1 equiv). To the resulting white suspension was added (*S*)-O-methylmandelic acid (93 mg, 0.56 mmol) and the mixture was stirred for 10 min. A solution of (±)-**14** (89 mg, 0.50 mmol) in pyridine (100 μL) and acetonitrile (500 μL) was then added slowly and the resultant mixture stirred at 0°C for 30 min. The pale yellow reaction mixture was diluted with Et_2O (100 mL), the organic phase was washed with sat. aq. $CuSO_4$, dried (Na_2SO_4) and concentrated. Purification and separation of the isomers by column chromatography (silica gel, hexane/EtOAc, 2/1) afforded 69 mg (43%) of **16** and 72 mg (44%) of **17**. Analytical data are reported for a distilled (**16**) or recrystallized (**17**) samples. Data for **16**: bp 150°C (4 x 10^{-5} Torr); ^{1}H NMR (300 MHz) 7.52-7.50 (m, 2 H, PhH), 7.39-7.32 (m, 3 H, PhH), 5.68 (d, J = 7.1, 1 H, HC(1)), 4.89 (s, 1 H, HC(2')), 3.95 (ddd, J = 11.9, 8.5, 3.4, 1 H, HC(4)), 3.49 (s, 3 H, OCH_3), 2.93 (dt, J = 11.9, 8.1, 1 H, HC(4)), 2.73 (q, J = 7.4, 1 H, HC(7a)), 2.30-2.22 (m, 1 H), 2.20-2.05 (m, 1 H), 1.81-1.71 (m, 1 H), 1.65-1.58 (m, 2 H, H_2C(7)), 1.44-1.56 (m, 1 H), 1.32 (s, 3 H, H_3C(8)); ^{13}C NMR (75.5 MHz) 170.46 (C=O, C(2)), 170.10 (C=O, C(1')), 135.82, 128.61, 128.44, 127.02, 82.54 (C(1)), 75.41 (C(7b)), 74.89 (C(2')), 57.55 (OCH_3), 49.38 (C(7a)), 49.30 (C(5a)), 42.49 (C(4)), 31.40 (C(5)), 31.27 (C(7)), 25.54 (C(6)), 21.13 (C(8)); IR (CCl_4) 2963 (m), 2872 (w), 2831 (w), 1721 (s), 1452 (w), 1329 (m), 1334 (w), 1242 (m), 1228 (m), 1202 (m), 1169 (m), 1116 (m), 909 (w); MS (70 eV) 329 (M^+, 1.81), 208 (10), 148 (15), 122 (68), 121 (100), 118 (11), 105 (22), 91 (36), 90 (11), 81 (11), 79 (11), 77 (62), 67 (12); Anal. Calcd for $C_{19}H_{23}NO_4$ (329.16): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.29; H, 7.05; N, 4.29; TLC R_f 0.24 (hexane/EtOAc, 1/1). Data for **17**: mp 99-100°C (hexane/EtOAc); ^{1}H NMR (300 MHz) 7.50-7.40 (m, 2 H, PhH), 7.40-7.26 (m, 3 H, PhH), 5.72 (d, J = 7.1, 1 H, HC(1)), 4.95 (s, 1 H, HC(2')), 3.94 (ddd, J = 11.9, 8.6, 3.3, 1 H, HC(4)), 3.45 (s, 3 H, OCH_3), 2.92 (dt, J = 11.9, 8.1, 1 H, HC(4)), 2.58 (q, J = 7.4, 1 H, HC(7a)), 2.22-2.18 (m, 1 H), 2.17-2.06 (m, 1 H), 1.62-1.55 (m, 1 H), 1.50-1.39 (m, 1 H), 1.23 (s, 3 H, H_3C(8)), 1.20-0.99 (m, 3 H, H_2C(7)+HC); ^{13}C NMR (75.5 MHz) 170.66 (C=O, C(2)), 169.74 (C=O, C(1')),

136.04, 128.69, 128.47, 127.26, 81.67 (C(1)), 75.39 (C(7b)), 74.74 (C(2')), 57.36 (OCH_3), 49.16 (C(7a)), 49.10 (C(5a)), 42.58(C(4)), 31.29 (C(5), C(7)) , 24.71 (C(6)), 23.09 (C(8)); IR (CCl_4) 2965 (m), 1761 (m), 1720 (s), 1392 (m), 1335 (w), 1263 (w), 1197 (m), 1170 (m), 1120 (m), 993 (w); MS (70 eV) 329 (M^+, 1.73), 148 (13), 122 (59), 121 (100), 105 (17), 91 (36), 90 (31), 90 (11), 77 (53), 55(15), 41 (16); TLC R_f 0.12 (hexane/EtOAc, 1/1); Anal. Calcd for $C_{19}H_{23}NO_4$ (329.16): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.09; H, 7.03; N, 4.13.

(1*S*,3*R*,5a*S*,7a*S*,7b*R*)-1-[(*S*)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxo-5a,6,7,7a-tetrahydrocyclopenta[1,2,3-*gi*]pyrrolidino[1,2-*a*]pyrrolidine (16). Following the procedure for the preparation of the mandelates **16** and **17** from (±)-**14**, combination of (-)-**14** (32 mg, 0.17 mmol), derived from hydrogenolysis of **13a**, and (*S*)-O-methylmandelic acid (29 mg, 0.17 mmol) produced only **16** (47 mg, 81%). The chromatographic and spectroscopic data for **16** were consistent with those for **16** isolated from the reaction of (±)-**14**.

Methyl (4*R*,6*R*)-2-(Z)-6-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-4,7,7-trimethylbicyclo-[2.2.1]heptan-2-oxy]-3-methyl-2-oxido-5,6-dihydro-4H-1,2-oxazine-4-hexenoate (18a) and Methyl (4*R*,6*S*)-2-(Z)-6[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-Dimethylpropoxy)-4,7,7-trimethylbicyclo-[2.2.1]-heptan-2-oxy]-3-methyl-2-oxido-5,6-dihydro-4H-1,2-oxazine-4-hexenoate (18b). To a magnetically-stirred, cold (-78°C) solution of **2** (300 mg, 1.41 mmol) in dichloromethane (2 mL) was added a solution of dichlorotitanium diisopropoxide (3.66 mmol, 2.6 equiv) in dichloromethane (3 mL). The pale brown solution was stirred at -78°C for 10 min and a solution of **6** (450 mg, 1.69 mmol, 1.2 equiv) in dichloromethane (2 mL) was added dropwise. The resulting mixture was stirred at -78°C for 14.5 h, quenched with 1.0 N NaOH in methanol (7 mL), and allowed to warm to room temperature. The white cloudy mixture was poured into dichloromethane (100 mL) and washed with water (3 x 50 mL). The aqueous layers were extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried ($MgSO_4$-$NaHCO_3$, 1/1) and concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel; hexane/EtOAc, 6/1-1/1) to afford 500 mg (74%) of **18a** and 86 mg (13%) of **18b** as clear viscous oils. Data for **18a**: ^{1}H NMR (300 MHz) 6.19 (dt, J = 11.5, 7.4, 1 H, HC(11)), 5.81 (d, J = 11.5, 1 H, HC(12)), 5.25 (t, J = 3.5, 1 H, HC(6)), 3.96 (d, J = 6.7, 1 H, HC(2')), 3.70 (s, 3 H, H_3C(14)), 3.21 (d, J = 6.7, 1 H, HC(3')), 3.11, 3.07 (ABq, J = 8.1, 2 H, H_2C(1")), 2.63 (m, 2 H, H_2C(10)), 2.40 (m, 1 H, HC(4)), 2.10 (m, 1 H, HC(5)), 2.07 (s, 3 H, H_3C(7)), 1.88 (dt, J = 14.1, 3.9, 1 H, HC(5)), 1.81-0.91 (m, 9 H), 1.05 (s, 3 H, CH_3), 0.90 (s, 12 H, 3 x H_3C(3"), CH_3), 0.74 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 166.43 (C(13)), 149.42 (C(11)), 124.19 (C(3)), 119.71 (C(12), 102.48 (C(6)), 88.32 (CH), 82.98 (C(1")), 82.87 (CH), 50.75 (C(14)), 49.75 (CH), 46.44 (C), 34.56 (C(4)), 32.25 (C), 31.23 (CH_2), 28.26 (CH_2), 28.09 (CH_2), 26.75 (CH_3), 26.05 (CH_2), 23.98 (CH_2), 20.56 (CH_3), 17.05 (C(7)), 11.54 (CH_3); IR (CCl_4) 2955 (s), 2870 (s), 1761 (w), 1725 (s), 1647 (m), 1615 (m), 1478 (m), 1460 (m), 1439 (m), 1408 (m), 1390 (m), 1371 (m), 1362 (m), 1266 (s), 1239 (m), 1200 (s), 1179 (s), 1120 (s), 1059 (m), 1015 (m), 982 (w), 907 (m), 843 (m); MS (70 eV) 240 (7), 153 (55), 135 (8), 123 (22), 121 (10), 109 (24), 95 (26), 93 (14), 81 (15), 71 (100), 69 (10), 67 (14), 55 (26), 43 (83), 41 (36); TLC R_f 0.24 (hexane/EtOAc, 1/1). Data for **18b**: ^{1}H NMR (300 MHz) 6.20 (dt, J = 11.4, 7.6, 1 H, HC(11)), 5.81 (d, J = 11.7, 1 H, HC(12)), 5.45 (s, 1 H, HC(6)), 4.18 (d, J = 6.7, 1 H, HC(2')), 3.70 (s, 3 H, H_3C(14)), 3.65 (d, J = 8.7, 1 H, HC(1")), 3.27 (d, J = 6.7, 1 H, HC(3')), 3.20 (d, J = 8.6, 1 H, HC(1")), 2.85 (t, J = 7.7, 2 H, H_2C(10)), 2.67 (m, 1 H, HC(4)), 2.03 (s, 3 H, H_3C(7)), 2.00-1.30 (m, 9 H), 1.06 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 0.86 (s, 9 H, 3 x H_3C(3")), 0.77 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 166.60 (C(13)), 149.24 (C(11)), 124.13 (C(3)), 120.05 (C(12)), 98.78 (C(6)), 88.33 (CH), 82.47 (C(1")), 81.58 (CH), 51.08 (C(14)), 49.50 (C), 47.47 (CH), 46.66 (C), 33.53 (CH), 33.14 (CH_2), 32.52 (C), 31.76 (CH_2), 30.21 (CH_2), 28.63 (CH_2), 25.49 (CH_2), 23.61 (CH_2), 21.08 (CH_3), 20.76 (CH_3), 16.96 (C(7)), 11.63 (CH_3); 1R (CCl_4) 2953 (s), 2869 (s), 1763 (m), 1726 (s), 1614 (m), 1478 (m), 1439 (m), 1385 (m), 1362 (m), 1266 (s), 1200 (s), 1150 (s), 1115 (s), 1065 (m), 1038 (m), 1003 (m), 965 (w), 908 (s), 833 (m); MS (70 eV) 240 (17), 169 (24), 153 (56), 135 (16), 123 (40), 109 (24), 95 (22), 93 (15), 81 (15), 71 (100), 67 (14), 55 (25), 43 (99), 40 (30); TLC R_f 0.39 (hexane/EtOAc, 1/1).

Methyl (1*S*,3*R*,5*S*,6a*S*,9a*R*,9b*R*)-5-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-9b-methylhexahydro-1H-isooxazolo[2,3,4-h][2,1]benzoxazine-1-carboxylate (19a). To a solution of **18a** (480 mg, 1 mmol) in toluene (15 mL) was added anhydrous sodium bicarbonate (25 mg). The mixture was stirred at ~40°C for 24 h. The mixture was filtered, concentrated *in*

vacuo, and the residue was purified by column chromatography (silica gel; hexane/EtOAc, 12/1-8/1) to afford 415 mg (86%) of **19a** as a white solid. Data for **19a**: ^{1}H NMR (300 MHz) 4.85 (d, J = 10.7, 1 H, HC(1)), 4.61 (dd, J = 9.5, 1.8, 1 H, HC(5)), 3.97 (d, J = 6.7, 1 H, HC(2')), 3.73 (s, 3 H, H_3C(12)), 3.24 (ddd, J = 13.0, 10.7, 3.2, 1 H, HC(9a)), 3.19 (d, J = 6.7, 1 H, HC(3')), 3.14, 3.09 (ABq, J = 8.1, 2 H, H_2C(1")), 2.13-2.00 (m, 2 H), 1.78 (d, J = 4.7, 1 H), 1.70 (m, 2 H), 1.60 (m, 2 H), 1.55-1.20 (m, 6 H), 1.15 (s, 3 H, H_3C(10)), 1.09 (s, 3 H, CH_3), 1.02-0.96 (m, 1 H), 0.89 (s, 12 H, 3 x H_3C(3"), CH_3), 0.73 (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz) 170.41 (C(11)), 100.16 (C(5)), 88.45 (C(1)), 83.16 (C(1")), 82.52 (CH), 79.45 (CH), 71.09 (C(9)), 51.88 (C(12)), 50.91 (CH), 49.92 (C), 46.63 (C), 40.36 (C(9a)), 37.34 (C(6a)), 33.49 (CH_2), 32.42 (C), 30.30 (C(6)), 26.92 (CH_3), 26.13 (CH_2), 24.18 (CH_2), 22.74 (CH_2), 22.08 (CH_2), 20.91 (CH_3), 20.70 (CH_3), 18.74 (C(10)), 11.80 (CH_3); IR (CCl_4) 2953 (s), 2868 (m), 1763 (m), 1736 (m), 1476 (w), 1449 (m), 1385 (w), 1362 (m), 1269 (w), 1198 (m), 1160 (s), 1109 (m), 1078 (m), 1061 (m), 999 (w), 837 (m); high resolution MS calcd for $C_{27}H_{46}NO_6$ (M^++H) 480.3325, found 480.3332; TLC R_f 0.39 (hexane/EtOAc, 5/1).

Methyl (1*S*,3*R*,5*R*,6a*S*,9a*R*,9b*R*)-5-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-oxy]-9b-methylhexahydro-1H-isooxazolo[2,3,4-h][2,1]benzoxazine-1-carboxylate (19b). To a solution of **18b** (80 mg, 0.167 mmol) in toluene (10 mL) was added sodium bicarbonate (25 mg). The suspension was stirred at 40°C for 6 h. The mixture was then filtered, concentrated and the residue was purified by column chromatography (silica gel; hexane/EtOAc, 10/1) to afford 62 mg (78%) of **19b** as a white solid. Data for **19b**: ^{1}H NMR (300 MHz) 5.09 (d, J = 3.5, 1 H, HC(5)), 4.84 (d, J = 10.7, 1 H, HC(1)), 4.19 (d, J = 6.8, 1 H, HC(2')), 3.75 (s, 3 H, H_3C(12)), 3.65 (d, J = 8.7, 1 H, HC(1")), 3.29 (d, J = 6.8, 1 H, HC(3')), 3.19 (ddd, J = 12.6, 10.4, 3.1, 1 H, HC(9a)), 2.87 (d, J = 8.6 1 H, HC(1")), 2.60-2.56 (m, 1 H), 2.11-2.06 (m, 1 H), 1.95 (td, J = 13.2, 3.8, 1 H, H(C(6)), 1.80-1.20 (m, 11 H), 1.17 (s, 3 H, H_3C(10)), 1.07 (s, 3 H, H_3C), 0.89 (s, 9 H, 3xH_3C(3)), 0.88 (s, 3 H, H_3C), 0.75 (s, 3 H, H_3C); ^{13}C NMR (75.5 MHz) 170.40 C(1)), 96.65 (C(5)), 88.44 (C(1)), 82.46 (C(1")), 79.59 (CH), 78.98 (CH), 71.75 (C(9b)), 52.02 (C(12)), 49.56 (CH), 46.59 (C), 46.00 (C), 40.57 (C(9a)), 33.92 (CH), 33.83 (CH_2), 32.64 (C), 27.36 (CH_2), 27.02 (CH_3), 25.84 (CH_2), 23.92 (CH_2), 22.93 (CH_2), 21.68 (CH_2), 21.28 (CH_3), 20.73 (CH_3), 19.14 (C(10)), 11.80 (CH_3); TLC R_f 0.84 (hexane/EtOAc, 1/1).

Hydrogenolysis of 19a. (1*S*,3*R*,5a*S*,8a*R*,8b*R*)-1-Hydroxy-8b-methyl-2-oxohexahydropyrrolidino[1,5,4-hj]indoline (1*S*)-(21). To a solution of **19a** (255 mg, 0.53 mmol) in methanol (10 mL) was added a catalytic amount of Raney nickel. The suspension was stirred under H_2 (160 psi) at room temperature for 18 h. The mixture was filtered through a celite pad, and concentrated. The residue was dissolved in toluene (10 mL) and stirred at 110°C for 26 h and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexane, hexane/EtOAc, 10/1-1/1) to afford 91 mg (88%) of (1*S*)-**21** as a white solid and 117 mg (91%) of recovered **3**. Data for (1*S*)-**21**: ^{1}H NMR (300 MHz) 4.38 (d, J = 11.1, 1 H, HC(1)), 3.88 (dd, J = 11.8, 7.5, 1 H, HC(4)), 3.30 (br, 1 H, HOC(1)), 2.97 (td, J = 11.9, 5.4, 1 H, HC(4)), 2.14 (quintet, J = 6.1, 1 H), 1.91-1.70 (m, 5 H), 1.58 (m, 2 H), 1.40-1.24 (m, 2 H), 1.20 (s, 3 H, H_3C(9)); ^{13}C NMR (75.5 MHz) 179.70 (C(2)), 73.41 (C(1)), 62.81 (C(8b)), 49.83 (C(8a)), 45.05 (C(4)), 43.05 (C(6)), 34.81 (CH_2), 25.97 (CH_2), 22.36 (C(10)), 19.51 (CH_2), 17.47 (CH_2); IR (CCl_4) 3362 (br, m), 2949 (s), 2876 (m), 1709 (s), 1469 (w), 1381 (m), 1337 (m), 1302 (m), 1283 (w), 1235 (w), 1207 (w), 1165 (m), 1132 (w), 1111 (m), 872 (w); MS (70 eV) 195 (M^+, 16), 181 (12), 180 (100), 162 (19), 152 (21), 150 (17), 137 (11), 124 (19), 109 (10), 107 (12), 98 (15), 97 (47), 96 (18), 95 (19), 93 (21), 91 (12), 84 (40), 79 (23), 70 (23), 67 (33), 57 (21), 55 (45), 53 (22), 43 (38), 41 (68), 39 (33); TLC R_f 0.15 (hexane/EtOAc, 1/1); $([\alpha]_D^{23}$ -113.4 (1.0 $CHCl_3$))

rac-(1*S*,3*R*,5a*S*,8a*R*,8b*R*)-1-[N-(3,5-dinitrophenyl)carbamoxy]-8b-methyl-2-oxohexahydropyrrolidino[1,5,4-hj]indoline (±)-22. HPLC Analysis of (±)-21. A solution of 3,5-dinitrobenzoylazide (8 mg, 0.034 mmol, 1.1 equiv) in toluene (5 mL) was heated to reflux for 10 min, and a solution of (±)-**21** (6 mg, 0.031 mmol) in toluene (1 mL) was added. The mixture was again heated to reflux for 10 min, cooled to room temperature and concentrated. The off-white solid was purified by column chromatography (silica gel; hexane/EtOAc, 3/1-2/1) to give 9 mg (75%) of (±)-**22** as a white solid. Data for (±)-**22**: ^{1}H NMR ($CDCl_3$) 9.60 (s, br, 1 H, HN), 8.63 (s, 1 H, HC(5')), 8.62 (s, 2 H, C(3')), 5.63 (d, J = 12.0, 1 H, HC(1)), 3.98 (dd, J = 12.0, 7.3, 1 H, HC(4)), 3.13 (td, J = 11.9, 5.4, 1 H, HC(4)), 2.29 (quintet, J = 5.9, 1 H, HC(5a)), 2.15-1.93 (m, 2 H), 1.81-1.61 (m, 4 H), 1.45-1.38 (m, 1 H), 1.35 (s, 3 H, H_3C(9)), 1.31-1.23 (m, 1 H); ^{13}C NMR ($CDCl_3$) 174.48 (C(2)), 152.76 (C(1')), 148.72 (C(4')), 141.13 (C(2')), 118.21 (C(5')), 112.55 (C(3')), 76.22 (C(1)), 63.35 (C(8b)), 48.66 (C(8a)), 45.58 (C(4)), 43.21 (C(6)), 35.15, 26.16, 22.56 (C(10)), 19.53, 17.74;

IR ($CDCl_3$) 2953 (m), 1696 (s), 1609 (m), 1549 (s), 1404 (m), 1347 (s), 1246 (s), 1221 (s), 1115 (m); TLC R_f 0.30 (hexane/EtOAc, 1/1); HPLC (Pirkle; hexane/EtOAc, 7/3, 1.5 mL/min) t_R (1*R*)-**22**, 8.04 min (48.58%); t_R (1*S*)-**22**, 29.24 min (51.42%).

HPLC Analysis of (-)-21 from 19a. A solution of 3,5-dinitrobenzoylazide (8 mg, 0.034 mmol, 1.1 equiv) in toluene (5 mL) was heated to reflux for 10 min, and a solution of (-)-**21** from **19a** (6 mg, 0.031 mmol) in toluene (1 mL) was added. The mixture was again heated to reflux for 10 min, cooled to room temperature and concentrated. The off-white solid was purified by column chromatography (silica gel; hexane/EtOAc, 3/1-1/1) to give 10 mg (83%) of (1*S*)-**22** as a white solid. Data for (1*S*)-**22**: ^1H NMR ($CDCl_3$) 9.57 (s, br, 1 H, HN), 8.63 (d, J = 1.51, 1 H, HC(5')), 8.62 (d, J = 1.38, 2 H, HC(3')), 5.63 (d, J = 12.0, 1 H, HC(1)), 3.99 (dd, J = 12.0, 7.3, 1 H, HC(4)), 3.12 (td, J = 11.9, 5.4, 1 H, HC(4)), 2.28 (quintet, J = 6.1, 1 H, HC(5a)), 2.15-1.93 (m, 2 H), 1.81-1.60 (m, 4 H), 1.45-1.40 (m, 1 H), 1.34 (s, 3 H, $H_3C(9)$), 1.32-1.23 (m, 2 H); ^{13}C NMR ($CDCl_3$) 174.46 (C(2)), 152.75 (C(1')), 148.72 (C(4')), 141.12 (C(2')), 118.20 (C(5')), 112.55 (C(3')), 76.22 (C(1)), 63.35 (C(8b)), 48.65 (C(8a)), 45.58 (C(4)), 43.21 (C(6)), 35.14 (CH_2), 26.16 (CH_2), 22.56 (C(10)), 19.53 (CH_2), 17.74 (CH_2); IR ($CDCl_3$) 2955 (m), 1696 (s), 1549 (s), 1347 (s), 1246 (m), 1221 (s), 1115 (m); TLC R_f 0.30 (hexane/EtOAc, 1/1); HPLC (Pirkle; hexane/EtOAc, 7/3; 1.5 mL/min) t_R (1*R*)-**22**, 8.34 min (0.46%); t_R (1*S*)-**22**, 28.49 min (99.54%).

(1*S*,3*R*,5a*S*,8a*R*,8b*R*)-1-[(*S*)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxohexahydropyrrolidino[1,5,4-hj]indoline (23) and (1*R*,3*S*,5a*R*,8a*S*,8b*S*)-1-[(*S*)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxohexahydropyrrolidino[1,5,4-hj]indoline (24). To a cold (0°C) solution of DMF (60 μL, 0.77 mmol, 1.5 equiv) in acetonitrile (2 mL) was slowly added oxalyl chloride (49 μL, 0.56 mmol, 1.1 equiv). The resulting mixture was treated with (*S*)-O-methylmandelic acid (94 mg, 0.56 mmol, 1.1 equiv) and the mixture was stirred at 0°C for 15 min. A solution of (±)-**21** (100 mg, 0.51 mmol, 1 equiv) in pyridine (83 μL, 1.0 mmol, 2 equiv) was then added slowly and the resulting mixture stirred at 0°C for 45 min. The reaction mixture was diluted with Et_2O (30 mL), and washed with sat. aq. $CuSO_4$ (2 x 25 mL), dired ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel; hexane/EtOAC, 3/1-2/1) to afford 75 mg (43%) of **23** and 79 mg (45%) of **24**. Data for **23**: mp 86-87°C (hexane/EtOAc); ^1H NMR ($CDCl_3$) 7.50 (m, 2 H, Ar), 7.35 (m, 3 H, Ar), 5.57 (d, J = 12.0, 1 H, HC(1)), 4.89 (s, 1 H, HC(2')), 3.88 (dd, J = 11.9, 7.4, 1 H, HC(4)), 3.50 (s, 3 H, H_3CO), 2.96 (td, J = 11.8, 5.4, 1 H, HC(4)), 2.18-2.03 (m, 2 H), 1.93-1.82 (m, 2 H), 1.75-1.62 (m, 1 H), 1.61-1.45 (m, 3 H), 1.42-1.26 (m, 2 H), 1.22 (s, 3 H, $H_3C(9)$); ^{13}C NMR (75.5 MHz) 173.10 (C(2)), 170.56 (C(1')), 135.96 (C), 128.75 (CH), 128.58 (CH), 127.13 (CH), 82.78 (C(2')), 75.47 (C(1)), 62.86 (C(8b)), 57.73 (OCH_3), 47.85 (C(8a)), 45.35 (C(4)), 43.38 (C(5a)), 34.91 (CH_2), 26.04 (CH_2), 22.65 (C(9)), 19.58 (CH_2), 17.67 (CH_2); IR (CCl_4) 2955 (m), 2878 (w), 1722 (s), 1375 (w), 1246 (w), 1235 (w), 1198 (w), 1167 (w), 1107 (m); MS (70 eV) 343 (M^+, 3), 299 (11), 284 (16), 222 (26), 178 (22), 166 (12), 148 (46), 122 (91), 121 (100), 118 (17), 105 (30), 91 (56), 90 (17), 81 (15), 77 (91), 67 (21), 55 (29), 53 (13), 51 (11); TLC R_f 0.26 (hexane/EtOAc, 1/1); Anal. Calcd for $C_{20}H_{25}NO_4$ (343.423): C, 69.95; H, 7.34. Found: C, 70.04; H, 7.32. Data for **24**: mp 140-141°C (hexane/EtOAc); ^1H NMR (300 MHz) 7.45 (m, 2 H), 7.33 (m, 3 H), 5.58 (d, J = 12.0, 1 H, HC(1)), 4.89 (s, 1 H, HC(2')), 3.87 (dd, J = 11.8, 7.4, 1 H, HC(4)), 3.44 (s, 3 H, H_3CO), 2.94 (td, J = 11.8, 5.4, 1 H, HC(4)), 2.11 (m, 1 H, HC(5)), 1.91-1.75 (m, 3 H), 1.58-1.22 (m, 4 H), 1.18 (s, 3 H, $H_3C(9)$), 1.15-1.05 (m, 2 H); ^{13}C NMR (75.5 MHz) 173.40 (C(2)), 170.34 (C(1')), 136.19 (C), 128.71 (CH), 128.53 (CH), 127.26 (CH), 82.02 (C(2')), 75.23 (C(1)), 62.78 (C(8b)), 57.51 (OCH_3), 48.02 (C(8a)), 45.34 (C(4)), 43.19 (C(5a)), 34.81 (CH_2), 22.57 (C(9)), 19.43 (CH_2), 17.33 (CH_2); IR (CCl_4) 2953 (m), 2878 (w), 1763 (m), 1723 (s), 1375 (m), 1198 (m), 1167 (m), 1119 (m); MS (70 eV) 343 (M^+, 3), 222 (17), 178 (15), 148 (28), 122 (59), 121 (100), 105 (9), 91 (32), 90 (10), 77 (56), 67 (13), 55 (18), 41 (21); TLC R_f 0.16 (hexane/EtOAc, 1/1); Anal. Calcd for $C_{20}H_{25}NO_4$ (343.423): C, 69.95; H, 7.34. Found: C, 69.74; H, 7.22.

(1*S*,3*R*,5a*S*,8a*R*,8b*R*)-1-[(s)-α-Methoxyphenylacetoxy]-7b-methyl-2-oxohexahydropyrrolidino[1,5,4-hj]indoline (23). To a cold (0°C) solution of DMF (15 μL, 0.19 mmol, 1.5 equiv) in acetonitrile (500 μL) was slowly added oxalyl chloride (13 μL, 0.141 mmol, 1.1 equiv). The resulting mixture was treated with (*S*)-O-methylmandelic acid (23 mg, 0.141 mmol, 1.1 equiv) and the mixture was stirred at 0°C for 15 min. A solution of (-)-**21** (25 mg, 0.128 mmol) in pyridine (20 μL, 0.256 mmol, 2 equiv) was then added slowly and the resulting mixture stirred at 0°C for 30 min. The mixture was diluted with diethyl ether (30 mL), and washed with sat. aq. $CuSO_4$(2 x 25 mL), dried ($MgSO_4$) and concentrated. The residue was purified by

column chromatography (silica gel; hexane/EtOAc, 3/1-1/1) to afford 35 mg (80%) of **23** as a white solid. Data for **23**: ^{1}H NMR ($CDCl_3$) 7.51 (m, 2 H, Ar), 7.35 m, 3 H, Ar), 5.58 (d, J = 12.2, 1 H, HC(1)), 4.90 (s, 1 H, HC(2')), 3.90 (dd, J = 11.9, 7.4, 1 H, HC(4)), 3.51 (s, 3 H, H_3CO), 2.97 (td, J = 11.9, 5.4, 1 H, HC(4)), 2.19-2.05 (m, 2 H), 1.94-1.85 (m, 2 H), 1.75-1.62 (m, 1 H), 1.60-1.47 (m, 2 H), 1.44-1.26 (m, 1 H), 1.23 (s, 3 H, H_3C(9)); ^{13}C NMR ($CDCl_3$) 173.15, 170.61, 135.99, 128.77, 128.61, 127.16, 82.81 (C(1)), 75.50, 62.89, 57.78, 47.89, 45.39, 43.42, 34.94), 26.08, 22.70, 19.61, 17.70; IR (CCl_4) 2955 (m), 2878 (w), 1723 (s), 1375 (m), 1246 (m), 1234 (m), 1200 (w), 1169 (w), 1107 (m); TLC R_f 0.26 (hexane/EtOAc, 1/1).

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