Hetero Diels−Alder vs Electrocyclic Reaction of Azadiene: Selective Synthesis of All Stereoisomers of Threonines

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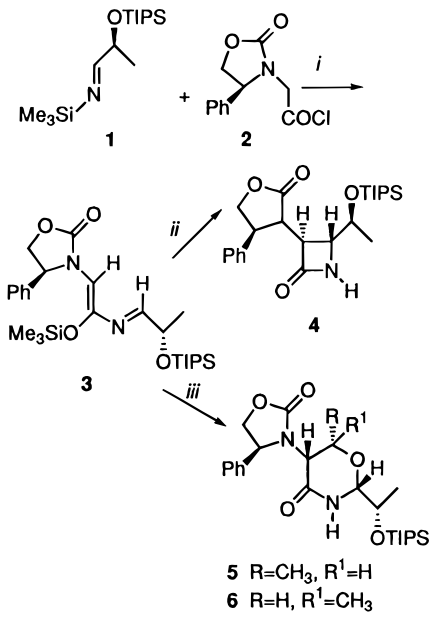
Recently, in conjunction with our current efforts on the use of *N*-(trimethylsilyl)imines[1] as useful tools in organic synthesis for the preparation of nitrogen-containing biologically active compounds, we have demonstrated the possibility of promoting a highly diastereoselective synthesis of trans-β-lactams via a two-step Staudinger reaction through the electrocyclic reaction of a stable 1-amido-2-[(trimethylsilyl)oxy]-3-aza-1,3-butadiene.[2] We have initiated a program to examine the utility of such azadienes in Diels−Alder reactions with the intent of generating precursors of β-hydroxy-α-amino acids, a biologically important class of compounds.[3]

The hetero Diels−Alder reaction using carbonyl compounds as dienophiles is a very useful method to construct heterocyclic rings and is widely used as a key step in the synthesis of natural products.[4] The use of activated dienes containing strong electron-donating groups, such as 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (Danishefsky's diene)[5] has found many applications since its introduction. In addition, Ghosez[6] recently reported on the synthesis and use of 2-aza-1,3-dienes as useful precursors of amino acids. In this paper we report our preliminary results on the synthesis of threonines and *allo*-threonines[7] via a hetero Diels−Alder reaction, using the azadiene **3** derived from the *N*-(trimethylsilyl)imine of (*S*)-lactic aldehyde **1** and acid chloride **2**.

Scheme 1[a]



[a] Reagents and conditions: (i) NEt_3, heptane; (ii) acetaldehyde, toluene, 100 °C; (iii) acetaldehyde, $BF_3{\cdot}Et_2O$, −78 °C, CH_2Cl_2.

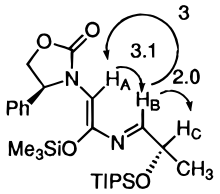


Figure 1. ^{1}H NMR NOE intensity changes, given as % value.

No reaction occurred on mixing the azadiene[2a] **3** with acetaldehyde in dichloro methane at room temperature. More drastic reaction conditions promote the formation of β-lactam **4** formed via an electrocyclic pathway. Addition of BF_3 resulted in [4 + 2] cycloaddition as has been observed by Danishefsky in his studies of hetero Diels−Alder reactions. This behavior, depicted in Scheme 1, can be rationalized on the basis of the following arguments. Electrocyclic and cycloaddition reactions require the presence of the diene in *s-cis* conformation. Results from NOE studies on compound **3** (Figure 1) are in agreement with the depicted structure since only in this structure are the H_A-H_B and H_B-H_C distances approximately the same. According to FMO theory,[8] the cycloaddition of the carbonyl dienophiles with 1,3-dienes are $HOMO_{diene}-LUMO_{dienophile}$ controlled processes. In the present case, replacement of C-2 of butadiene by a nitrogen atom lowers the HOMO (Table 1), thus lowering

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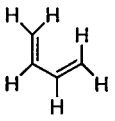
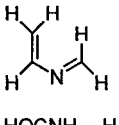
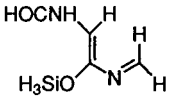
Table 1. AM1 Frontier Orbital Energies* (eV)

Compound	LUMO	HOMO
	0.46	**-9.35**
	0.14	**-9.91**
	-0.23	**-8.38**
CH_3CHO	**0.84**	-13.95
$CH_3CHO\ BF_3$	**-0.36**	-13.65

*AM1 Calculations were performed on optimized geometries.[11]

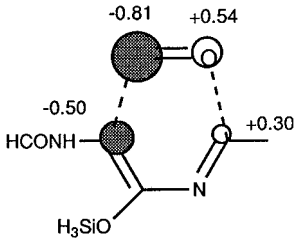
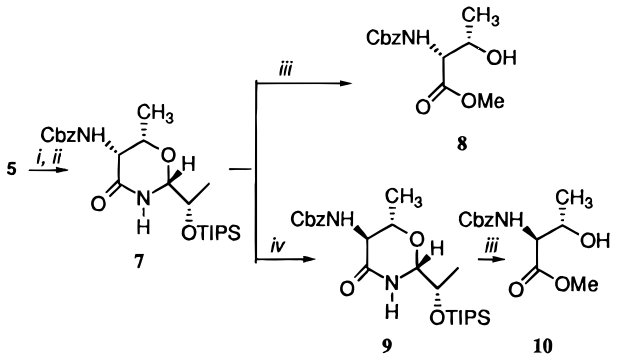


Figure 2. HOMO−azadiene and LUMO−acetaldehyde BF_3 interacting coefficients.

the reactivity of this 2-azadiene in [4 + 2] cycloaddition reactions. It is the simultaneous introduction of a silyloxy group and an amidic nitrogen into the azadiene skeleton that raises the E_{HOMO} with respect to both the unsubstituted butadiene and the unsubstituted 2-azadiene. This increase in the HOMO orbital energy increases the reactivity in a [4 + 2] intermolecular cycloaddition as well as in electrocyclic ring closure to give the azetidinone.[2] To favor the [4 + 2] cycloaddition, it is therefore necessary to increase the reactivity of the dienophile. This is accomplished by complexation of the dienophile with a Lewis acid, which significantly lowers its LUMO energy. The regioselectivity of the reaction is controlled by the relative magnitude of the atomic orbital coefficients, according to the large−large rule, as depicted in Figure 2.

Treatment of the intermediate **3** (Scheme 1) with acetaldehyde in the presence of BF_3 etherate in methylene chloride at −78 °C for 3 h followed by an age overnight at rt afforded the corresponding tetrahydro-1,3-oxazin-4-one **5** in 66% yield (based on the starting (*S*)-(triisopropylsiloxy)lactaldehyde) contaminated by 7% of the diastereoisomer **6**. Quenching of the reaction mixture at −78 °C after 3 h did not change the diastereomeric ratio but gave a lower yield (50%). After chromatographic purification, one-pot−two-step removal of the Evans' oxazolidinone[9] and in situ formation of the corresponding *N*-Cbz derivative, the oxazin-4-one **7** was obtained in 67% yield. Ring opening of this product by methanolic HCl furnished the (D)-*N*-Cbz-threonine methyl ester **8** in 90% yield (39% overall yield calculated on starting (*S*)-lactaldehyde) (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (i) Li/NH_3, −78 °C; (ii) CbzCl, acetone, $NaHCO_3$; (iii) HCl/MeOH; (iv) DBU/DMF, 80 °C.

Starting from the (*R*)-lactimine ***ent*-1** and (*R*)-oxazolidinone ***ent*-2** and following the same protocol the natural L-*N*-Cbz-threonine methyl ester ***ent*-8** was obtained in 41% overall yield.

Next we undertook the synthesis of L and D enantiomers of the *allo*-threonines **10** and ***ent*-10**, respectively (Scheme 2). This was readily accomplished by epimerization of the C-5 stereogenic center of **7** and ***ent*-7** at C-5 with DBU in DMF (80 °C, 3 h) and then elaboration of the products so obtained to the *allo*-threonines using the protocol already described. The optical rotations of the threonines and *allo*-threonines Cbz-methyl esters obtained by our procedure are close to those reported in the literature (see Experimental Section).

The observed diastereomeric ratio of **5** and **6** conforms with the *endo*−*exo* selectivity found by Danishefsky in similar hetero Diels−Alder reactions.[10] Moreover, it is worth noting that whereas the use of (*S*)-lactaldehyde and (*S*)-Evans auxiliary resulted in a complete diastereofacial selectivity, preliminary results have shown that this selectivity is lost when a different couple of aldehyde and chiral auxiliary are used (e.g. (*S*)-(triisopropylsiloxy)-lactaldehyde and (*R*)-4-phenyl-2-oxazolidinone). Attempts to improve the diastereomeric ratio by the use of different Lewis acids have so far failed (e.g., $ZnCl_2$ gave a decrease in yield and diastereoselectivity). More systematic studies on these aspects as well as on the use of other aldehydes are currently in progress and will be described in due course.

Experimental Section

General Methods. All solvents were dried and stored over 4 Å molecular sieves prior to use and had no more than 25 ppm of H_2O as measured by Karl-Fisher titration. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with Merck F_{254} silica gel 60 and visualized by UV light, ammonium phosphomolybdate spray, or iodine stain. Column chromatography was performed with mixtures of methylene chloride/acetone on Merck silica gel 60. All reactions were performed under a dry argon or nitrogen atmosphere in base-washed, flame-dried glassware. Optical rotation measurements were recorded at room temperature. NMR spectra were determined at 200 or 300 MHz for ^1H and 50 and 75 MHz for ^{13}C in $CDCl_3$ solution using the solvent as internal standard. Mass spectra were determined at 70 eV.

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Starting Materials. (*S*)- and (*R*)-lactaldehyde were prepared according the reported procedure.[1a]

(2*R*,5*R*,6*S*)-2-[(*S*)-1-[(Triisopropylsilyl)oxy]ethyl]-5-[(*S*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-6-methylperhydro-1,3-oxazin-4-one and (2*R*,5*R*,6*R*)2-[(*S*)-1-[(Triisopropylsilyl)oxy]-ethyl]-5-[(*S*)-2-oxo-4-phenyl-3-oxazolidin-3-yl]-6-methyl-perhydro-1,3-oxazin-4-one (5 and 6). The acyl chloride **2** was prepared as described by Evans.[9] To a solution of the corresponding commercially available acid (0.26 g, 1.2 mmol) in dry toluene (5 mL) was added oxalyl chloride (0.16 mL, 1.8 mmol) in one portion, and the mixture was warmed to 60 °C for 3 h. The solvent and excess oxalyl chloride were removed in vacuo, and the resulting crude acid chloride **2** was redissolved in toluene (5 mL). Meanwhile, a solution of (*S*)-lactimine **1** was prepared by the dropwise addition of a heptane solution (5 mL) of (*S*)-1-(triisopropylsiloxy)lactaldehyde (0.23 g, 1 mmol) to a cooled (0 °C) THF solution of lithium bis(trimethyldisilyl)amide (LHMDSA) (1 mL of a 1 M solution in THF). After the addition of the aldehyde was complete, the reaction mixture was stirred at 0 °C for 15 min and at rt for 1 h. The formation of the imine was confirmed by an infrared spectrum of the reaction mixture (ν_{CN} = 1685 cm^{-1}). The imine solution was then warmed to rt, trimethylsilyl chloride (0.13 mL, 1 mmol) was added in one portion, and this mixture was allowed to stir for 1 h at rt. This same mixture was cooled to 0 °C, and triethylamine (0.3 mL, 2.0 mmol) was added in one portion. After this mixture was stirred for 5 min at 0 °C, the toluene solution of **2** was added very *slowly* (over 5 min). Stirring was maintained for 30 min at 0 °C and 1 h at rt. This yellow-orange mixture was then filtered through Celite, and the solvent was removed in vacuo. A small sample was removed from the reaction mixture and concentrated to an oil, and an ^{1}H NMR of this sample was run to check for the presence of the azadiene species **3**. The so obtained **3** was dissolved in methylene chloride (5 mL) and cooled at −78 °C, and acetaldehyde (0.11 mL, 2 mmol) in methylene chloride (2 mL) was added followed by a very slow addition of boron trifluoride diethyl etherate (0.12 mL, 1 mmol) dissolved in methylene chloride (10 mL). The reaction was stirred at −78 °C for 3 h and then allowed to warm to rt overnight. The crude reaction mixture was diluted with methylene chloride (10 mL), poured into a satured $NaHCO_3$ aqueous solution, and extracted with more methylene chloride. The organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude reaction mixture was purified by flash chromatography on silica gel eluting with methylene chloride/acetone 9/1. Compounds **5** and **6** were obtained in 66 and 7% yields, respectively, as oils. **5**: $[\alpha]^{20}_D$ = +113.5 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 1758, 1684, 1521 cm^{-1}; ^{1}H NMR 7.33 (s, 5H), 6.20 (s, 1H), 5.10 (dd, 1H, *J* = 6.1, 8.6), 4.72 (d, 1H, *J* = 3.7), 4.62 (t, 1H, *J* = 8.6), 4.15−4.07 (m, 2H), 4.05−3.90 (m, 2H), 1.28 (d, 3H, *J* = 6.5), 1.00 (m, 24H); ^{13}C NMR 165.8, 158.7, 137.4, 129.0, 128.6, 127.5, 86.1, 75.0, 70.6, 68.6, 61.5, 55.9, 17.9, 17.8, 16.3, 12.1; MS *m*/*z* 433 (M^+ − 43), 389, 275, 186, 106. Anal. Calcd for $C_{25}H_{40}N_2O_5Si$: C, 62.99; H, 8.46. Found: C, 62.87; H, 8.45.

6: $[\alpha]^{20}_D$ = +66.6 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 1759, 1684, 1521 cm^{-1}; ^{1}H NMR 7.40 (s, 5H), 6.28 (s, 1H), 5.15 (dd, 1H, *J* = 8.6, 9.8), 4.83 (m, 2H), 4.70 (t, 1H, *J* = 8.6), 4.20 (dd, 1H, *J* = 8.6, 9.8), 4.06 (dq, 1H, *J* = 4.5, 6.1), 3.05 (d, 1H, *J* = 8.8), 1.21 (d, 3H, *J* = 6.1), 1.08 (d, 3H, *J* = 6.1), 1.02 (s, 21H); ^{13}C NMR 168.0, 158.6, 136.5, 129.6, 129.2, 128.3, 82.9, 70.5, 69.5, 67.6, 63.9, 58.6, 18.6, 18.0, 18.0, 17.3, 12.3; MS *m*/*z* 433 (M^+ − 43), 389, 275, 186, 106. Anal. Calcd for $C_{25}H_{40}N_2O_5Si$: C, 62.99; H, 8.46. Found: C, 63.19; H, 8.47.

(2*S*,5*S*,6*R*)-2-[(*R*)-1-[(Triisopropylsilyl)oxy]ethyl]-5-[(*R*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-6-methylperhydro-1,3-oxazin-4-one and (2*S*,5*S*,6*S*)2-[(*R*)-1-[(Triisopropylsilyl)oxy]-ethyl]-5-[(*R*)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-6-methylperhydro-1,3-oxazin-4-one (*ent*-5 and *ent*-6). Following the same procedure described for **5** and **6**, ***ent*-5** and ***ent*-6** were obtained starting from (*R*)-(triisopropylsiloxy)lactaldehyde and (*R*)-oxazolidinone (66% yield, 90/10 diastereomeric ratio ***ent*-5/*ent*-6**). ***ent*-5:** $[\alpha]^{20}_D$ = −112.7 (*c* 0.70, $CHCl_3$). ***ent*-6**: $[\alpha]^{20}_D$ = −65.4 (*c* 0.70, $CHCl_3$).

(2*R*,5*R*,6*S*)-2-[(*S*)-1-[(Triisopropylsilyl)oxy]ethyl]-5-[(benzyloxycarbonyl)amino]-6-methylperhydro-1,3-oxazin-4-one (7). A THF/*t*-BuOH (10:1, 6 mL) solution of **5** (0.476 g, 1 mmol) was added at −78 °C to a solution of Li (42 mg, 6 mmol) in NH_3 (21 mL). The excess of Li was quenched after 2 min by the addition of solid NH_4Cl (0.32 g, 6 mmol), and the ammonia was allowed to distill off at −33 °C under a stream of N_2. The resulting crude product was dried in vacuo, dissolved in 5 mL of H_2O, briefly acidified to pH 3 with the addition of 10% aqueous HCl, and subsequently made basic (pH 8) with the addition of solid $NaHCO_3$. Benzylchloroformate (0.43 mL, 3 mmol) was added to the aqueous mixture. After 4 h, the reaction mixture was extracted with ethyl acetate, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, CH_2Cl_2/acetone 9/1) afforded **7** (0.33 g, 67%) as an oil: $[\alpha]^{20}_D$ = +10.6 (*c* 2.03, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1723, 1685, 1510, 1437. ^{1}H NMR 7.35 (s, 5H), 6.35 (s, 1H), 5.15 (m, 3H), 4.90 (d, 1H, *J* = 3.4), 4.38 (dd, 1H, *J* = 3.5, 9.15), 4.10 (m, 2H), 1.22 (d, 3H, *J* = 6.3), 1.12 (d, 3H, *J* = 6.1), 1.04 (s, 21H); ^{13}C NMR 167.9, 156.4, 136.2, 128.6, 128.3, 128.2, 84.2, 73.5, 68.3, 67.4, 54.3, 18.0, 18.0, 16.2, 15.9, 12.3; MS *m*/*z* 464 (M^+), 421 (M^+ − 43), 377, 287, 186. Anal. Calcd for $C_{24}H_{40}N_2O_5Si$: C, 62.03; H, 8.68. Found: C, 62.23; H, 8.70.

(2*S*,5*S*,6*R*) 2-[(*R*)-1-[(Triisopropylsilyl)oxy]ethyl]-5-[(benzyloxycarbonyl)amino]-6-methylperhydro-1,3-oxazin-4-one (*ent*-7). This compound was obtained by following the above-reported procedure for **7** starting from ***ent*-6**: $[\alpha]^{20}_D$ = −11.2 (*c* 1.63, $CHCl_3$).

D-Threonine *N*-(Carbobenzyloxy)methyl Ester 8. Compound **7** (0.2 g, 0.43 mmol) was dissolved in MeOH (20 mL). The solution was cooled at 0 °C, and 5 mL of a previously prepared satured solution of HCl in MeOH was added. After 30 min the solvent was removed in vacuo, a satured solution of $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate. A simple filtration on silica gel (CH_2Cl_2/acetone 9/1) yielded the target compound **8** in almost quantitative yield. Spectral data of this compound are superimposable with the authentic, commercially available (Aldrich), enantiomer: $[\alpha]^{20}_D$ = +18.0 (*c* 1.19 CH_3OH); mp 90 °C; IR ($CHCl_3$) 3450, 1725, 1520, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.30 (s, 5H), 5.72 (d, 1H, *J* = 8.5), 5.07 (s, 2H), 4.30 (m, 2H), 3.69 (s, 3H), 2.57 (bs, 1H), 1.17 (d, 3H, *J* = 6.5).

L-Threonine *N*-(Carbobenzyloxy)methyl Ester *ent*-8. This compound was obtained from ***ent*-7** by following the same procedure as described for **7**: $[\alpha]^{20}_D$ = −17.00 (*c* 1.33 CH_3OH).

Isomerization of Compound 7 To Give 9. Compound **7** (0.11 g, 0.237 mmol) was treated with DBU (0.036 g, 0.237 mmol) in DMF (3 mL) at 80 °C; after the TLC spot-test (CH_2Cl_2/acetone 9/1) showed complete disappearance of the starting material (overnight), the reaction mixture was poured in sodium acetate buffer (pH 5) (5 mL) and extracted with ethyl acetate. Removal of the solvent yielded the target compound **9** in quantitative yield: $[\alpha]^{20}_D$ = −25.00 (*c* 1.04 $CHCl_3$); IR ($CHCl_3$) 1728, 1686, 1518 cm^{-1}; ^{1}H NMR 7.33 (s, 5H), 6.28 (s, 1H), 5.47 (d, 1H, *J* = 7.8), 5.11 (s, 2H), 4.95 (bs, 1H), 4.03 (dq, 1H, *J* = 3.2, 6.1), 3.83 (m, 2H), 1.32 (d, 3H, *J* = 5.9), 1.14 (d, 3H, *J* = 6.1), 1.04 (s, 21H); ^{13}C NMR 168.9, 156.8, 136.2, 128.5, 128.1, 128.0, 85.1, 74.1, 68.8, 67.2, 56.5, 18.8, 18.0, 18.0, 15.6, 12.2; MS *m*/*z* 464 (M^+), 421, 377, 276, 187, 91. Anal. Calcd for $C_{24}H_{40}N_2O_5Si$: C, 62.03; H, 8.68. Found: C, 62.17; H, 8.69.

Compound *ent*-9. This compound was obtained in quantitative yield starting from ***ent*-7** by following the procedure reported for **9**: $[\alpha]^{20}_D$ = +24.00 (*c* 0.85 $CHCl_3$).

D-*allo*-Threonine *N*-(Carbobenzyloxy)methyl Ester 10. This compound was obtained in quantitative yield starting from **9** and following the procedure reported for **8**. Spectral data were superimposable with the reported ones: $[\alpha]^{20}_D$ = −14.2 (*c* 1.12 $CHCl_3$) (lit.[7e] = −14.5 (*c* 10 $CHCl_3$); mp 55 °C; IR ($CHCl_3$) 1700, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 5.67 (d, 1H, *J* = 8.2), 5.13 (s, 2H), 4.43 (dd, 1H, *J* = 8.0, 3.6), 4.15 (m, 1H), 3.77 (s, 3H), 2.0 (bs, 1H), 1.19 (d, 3H, *J* = 6.5).

L-*allo*-Threonine *N*-(Carbobenzyloxy)methyl Ester *ent*-10. This compound was obtained, in quantitative yield, following the same procedure as described for **10**: $[\alpha]^{20}_D$ = +14.0 (*c* 0.85 $CHCl_3$).

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