# A Study of the 3,3-Sigmatropic Rearrangement of Chiral Trichloroacetimidic Esters

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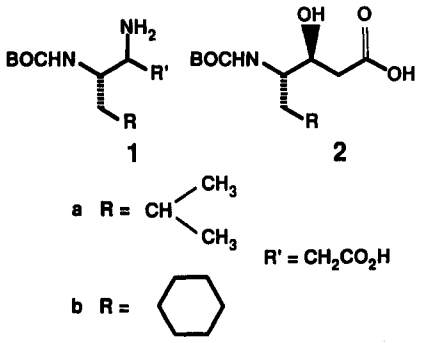
## Introduction

As part of an ongoing renin inhibitor program[1-3] a general synthesis of the noncleavable transition-state isostere **1** was required. The 3-aminodeoxystatine group **1a** has been used previously by others[4-6] and acts as a structural analogue of the tetrahedral species formed during enzymatic hydrolysis of a peptide bond. Peptides that contain this 3-aminodeoxystatine group have been prepared to study the importance of hydrogen bonding and electrostatic interaction when the 3(*S*)-hydroxyl group of BOC-statine **2a** or the cyclohexylmethyl analogue of statine **2b** is replaced by a basic amino group.




We initially carried out a synthesis to obtain both diastereomers of **1b** in protected form (compound **5**). Subsequent derivatization as has been reported previously[6] allowed assignment of the stereochemistry by an NOE experiment.

A novel route to 3-aminodeoxystatine derivatives via intermediate **4**, employing the 3,3-sigmatropic shift of a trichloroacetimidic ester, has been developed. It has been found possible to perform this Overman rearrangement[7-12] under *palladium catalysis*, in addition to a variety of other conditions. The conditions under which this reaction is performed have been found to affect the degree of stereoselectivity observed.

## Results and Discussion

The synthesis of key intermediate **5** from *N*-BOC-L-phenylalaninal[13-15] (Scheme I) was carried out via a route described previously for the statine analogue by Harris and co-workers.[6] Thus aldehyde **3** underwent a Wittig reaction with (carbethoxymethylene)triphenylphosphorane to afford $\alpha,\beta$-unsaturated ester **4** in good yield (75%) and with high trans selectivity, as expected (95:5 *E*/*Z*). Conjugate addition of ammonia under pressure (bomb, 80 °C, 7 h) followed by reaction with benzyl chloroformate under Schotten–Baumann conditions gave intermediate **5** as a mixture of diastereomers. These isomers were separated by fractional crystallization and converted separately to the cyclic ureas **6A** and **6B**. The stereochemistry of **6A** and **6B** was determined by spin decoupling and NOE studies. Thus, a close contact between the methylene group $\alpha$ to the ester and protons H-2 and H-3 was observed in the (2*S*,3*S*) isomer **6B**, while only to H-2 in the (2*R*,3*S*) isomer **6A**. In addition, the coupling constant ($^3J_{2,3}$ = 5.4 Hz) between H-2 and H-3 in the trans isomer **6B** can be contrasted with the expected larger coupling constant ($J$ = 7.8 Hz) in the cis isomer **6A** which is consistent with values reported previously for the trans and cis isomers of oxazolidinone analogs.[16-18] In the second route, intermediate **4** was treated with DIBAL and $BF_3$·$OEt_2$ to affect a 1,2-reduction to the allylic alcohol **7**. Reduction in the absence of the Lewis acid was nonselective and gave mixtures of **7** and the fully saturated alcohol. It has been suggested that the nitrogen lone pair can coordinate with DIBAL to assist in the 1,4-reduction of the $\alpha,\beta$-unsaturated system.[19] This was prevented by prior coordination of the nitrogen with the Lewis acid $BF_3$·$OEt_2$.

Alcohol **7** was deprotonated and treated with trichloroacetonitrile at 0 °C to produce the intermediate trichloroacetimidic ester **8**. Heating of this relatively unstable compound in xylenes for 36 h effected the Overman rearrangement to afford compound **9AB** which could be deprotected in aqueous base[20] to the deoxyaminostatine derivative **10**. It was expected that the presence of the chiral center $\alpha$ to the point of bond formation should

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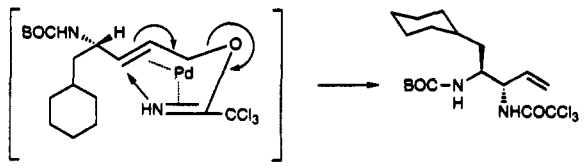


**Figure 1.** Palladium-catalyzed 3,3-sigmatropic rearrangement.

**Scheme I**

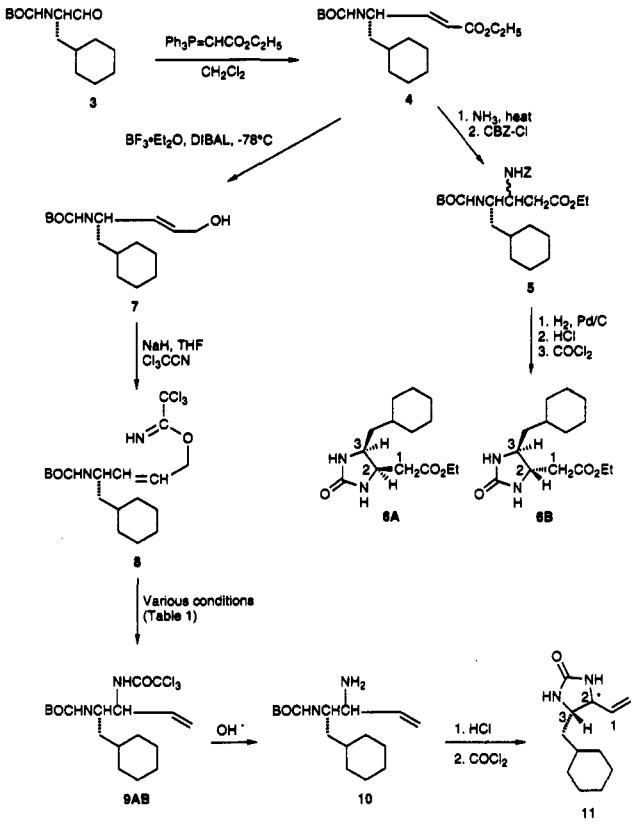


**Table I. Outcome of the Overman Rearrangement under Different Experimental Conditions**

| condns (R = $CH_2$-cyclohexyl) | comments |
|---|---|
| $I_2$, rt, 48 h | no reaction |
| NBS, THF | several products |
| Hg $(OCOCF_3)_2$, $NaBH_4$ | several products |
| Pd $(OCOCF_3)_2$, THF | one isomer |
| Pd $(OAc)_2$, THF | one isomer |
| Δ, xylenes | 45:55 mixture of isomers |

influence the stereochemical outcome of this reaction. The nitrogen should attack the least hindered face of the double bond via a chairlike transition state (Figure 1).

We have investigated a range of conditions to promote this 3,3-sigmatropic shift, and the results are shown in Table I. The stereochemistry of the single isomer obtained from the palladium-promoted Overman rearrangement was determined by conversion of **10** to the cyclic urea **11** (Scheme I) followed by measurement of proton coupling constants.

Irradiation of the H-1 multiplet (C*H* = $CH_2$) in **11** resulted in collapse of the H-2 signal to a broad singlet, indicating $^3J_{2,3}$ was less than ca. 2 Hz. This small scalar coupling indicates a near 90° dihedral angle between H-2 and H-3 which is consistent only with the trans relationship of the two protons. The stereochemistry at C-3 is known to be *S*; therefore, the absolute configuration at C-2 in **11** is also *S*.

In order to further investigate the effect of the cis/trans relationship of the C2 and C3 substituents on the H2–C2–C3–H2 torsion angle, models for *cis*- and *trans*-**11** were built using the Sybyl molecular modeling package (Tripos Associates). Both models were energy minimized and subjected to 10 ps of molecular dynamics simulation at 500 K using a Tripos-modified White–Vinter force field, ignoring electrostatics. Structures were written out every 10 fs. The resulting structures were then analyzed to investigate the torsional preference for the C2–C3 bond. The results suggest that the cis and trans isomers exhibit a distinct preference for a H2–C2–C3–H3 torsion angle of 10 ± 50° and 130 ± 50°, respectively (supplementary material). Of the two diastereoisomers, only the trans (*S,S*) isomer spent a significant amount of time with a H2–C2–C3–H3 torsion angle near 90°, consistent with the observed $^3J_{H2,H3} \leq 2$ Hz. Under the conditions used in these calculations, it is energetically prohibitive for the cis isomer to adopt a similar torsion angle. The latter observation is intuitively satisfying considering the large amount of ring strain resulting from forcing cis vicinal protons to adopt a near 90° torsion angle in this type of system. Previously reported coupling constants of analogous oxazolidinone derivatives indicate that smaller $^3J_{2,3}$ are invariably observed for trans substituents (ca. 4 Hz) than for cis substituents (ca. 8 Hz).[16-18] In comparison with the oxazolidinone analogs and compounds **6A** and **6B**, the smaller $^3J_{2,3(trans)}$ measured for **11** may, in part, be due to the different electronic nature of the vinyl substituent or to nonbonded interactions between the specific substituents in **11** that force the H2–C2–C3–H3 torsion angle to be near 90°.

The observed stereoselectivity of the palladium-catalyzed Overman rearrangement is difficult to explain based only on the steric bulk of the substituents α to the point of bond formation (BOC and cyclohexylmethyl). It can be postulated that the Pd catalyst may form a complex coordinating to both the imine and olefin bonds shielding one face of the double bond. Nucleophilic attack might be expected to occur antiperiplanar to the heteroatom containing functionality (NHBOC) giving rise to the observed stereochemistry. It would be interesting to investigate the effect of alternative protecting groups on the nitrogen and also other substituents at the α carbon with different steric constraints to provide a clearer understanding of the possible mechanism(s) involved. In summary, we have developed a novel stereoselective palladium-catalyzed route to a dipeptide transition-state isostere. Further studies are currently in progress investigating other metals and substrates in an attempt to attain a better understanding of the source of the stereoselectivity and the scope of this interesting reaction.

## Experimental Section

**General Procedures.** All reactions were carried out under $N_2$. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Analytical TLC was performed on Merck kieselgel 60 $F_{254}$ plates, visualizing with the use of ninhydrin spray. Column chromatography on kieselgel 60 silica gel (70–230 mesh or 230–400 mesh for flash) was used to purify all compounds. NOE difference spectra were obtained by saturating the peak of interest with a presaturation pulse during a 5-s relaxation delay between transients. The resulting data were subtracted from a spectrum in which the decoupler was placed in an unoccupied region. Individual components of each multiplet were irradiated in a time-shared manner with the

minimum power required to reduce the peak to <5% of its original intensity. $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, and $Hg(OCOCF_3)_2$ catalysts were purchased from Aldrich Chemical Co. All other reagents were purchased from Aldrich unless otherwise noted.

**Ethyl [S-(*E*)]-5-Cyclohexyl-4-[[(1,1-dimethylethoxy)carbonyl]amino]-2-pentenoate (4).** Title compound **4** was prepared from *N*-BOC-cyclohexylmethylalaninal[12,13] **3** as described previously[15]: m.p. 52-53°C.

**Ethyl γ-[[(1,1-Dimethylethoxy)carbonyl]amino]-β-[[(phenylmethoxy)carbonyl]amino]cyclohexanepentanoate (5).** A solution of the ester **4** (11.68 g, 0.036 mol) in ethanolic ammonia was heated in a sealed vessel at 80–90 °C for 16 h. The reaction mixture was then concentrated and the crude product eluted through a flash column (silica gel) with 4:1 ethyl acetate/hexane to afford the Michael adduct as a yellowish oil (7.20 g, 59%) (TLC: $R_f$ = 0.33, 4:1 ethyl acetate/hexane).

The mixture of diastereomeric amino esters (7.20 g, 0.021 mol), $NaHCO_3$ (5.4 g, 0.063 mol), and CBZ-Cl (6.4 mL, 0.32 mol) in 70 mL of $H_2O$ was stirred overnight at rt. After 15 h, diethyl ether was added and the solution was stirred until all solids were dissolved. The organic layer was separated, washed with saturated $NaHCO_3$, dried ($Na_2SO_4$), filtered, and concentrated. The diastereomers of **5** were first isolated by column chromatography on silica gel eluting with a gradient of 9:1–7:3 hexane/ethyl acetate. The oil thus obtained (11.6 g, 64%) was then repurified by flash chromatography on silica gel eluting with 7:3 hexane/ethyl acetate. Complete separation of the isomers was unsuccessful. However, a small amount of the slow isomer **5** was isolated as a white crystalline solid (4.53 g, 34%): mp 125–126 °C; $[\alpha]^{25}D$ = −4.69° (MeOH, $c$ = 0.013); TLC $R_f$ = 0.46 in 3:2 diethyl ether/hexane. Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.77; H, 8.63; N, 5.77. The remaining oil was dissolved in hexane and upon standing the fast isomer did precipitate from solution, TLC $R_f$ = 0.59 in 3:2 diethyl ether/hexane: mp 83–85 °C; $[\alpha]^{23}D$ = −39.7 (MeOH, $c$ = 0.015); MS (CI) $m/z$ 477 ($MH^+$), 377 ($MH^+$ − BOC). Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.89; H, 8.66; N, 5.94.

**Ethyl (4*R*-*cis* and 4*S*-*trans*)-5-(Cyclohexylmethyl)-2-oxo-4-imidazolidineacetate (6A and 6B).** A solution of the slow or fast isomer of **5** (1.0 g, 2.10 mmol) and 20% Pd/C catalyst (0.10 g) in EtOH (75 mL) was shaken on a Parr apparatus under $H_2$ for 28 h. The reaction mixture was filtered and the filtrate concentrated to a clear oil (0.72 g) utilized directly in the next step. HCl gas was bubbled through a solution of the amino ester in $CHCl_3$ (50 mL) for 20 min at rt. After 25 min of stirring the reaction mixture was gently heated on a steam bath for 5–10 min and then washed with saturated $NaHCO_3$ solution. The organic layer was dried ($Na_2SO_4$), filtered, and evaporated. The resulting crude diamine was taken up in 12.5% phosgene in toluene (12.5 mL) and stirred at rt overnight. The reaction mixture was concentrated and the residue dissolved in ethyl acetate. After being washed with saturated $NaHCO_3$ solution, the solution was dried ($Na_2SO_4$), filtered, and evaporated. The cyclic urea (**6A** or **6B**) was isolated by flash chromatography eluting with 5% MeOH in $CHCl_3$ to afford the product as an oil (0.20 g). **6A** (slow isomer): $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.27 (t, $J$ = 7.1 Hz, 3 H), 0.90–1.90 (m, 13 H), 2.47 (dd, $J$ = 9.7, 3.2 Hz, 1 H), 2.59 (dd, $J$ = 16.6, 9.4 Hz, 1 H), 3.96(H3) (m, $^3J_{2,3}$ = 7.8 Hz, 1 H), 4.06 (H2) (m, $^3J_{3,2}$ = 7.8 Hz, 1 H), 4.16 (q, $J$ = 7.1 Hz, 2 H), 5.07 (s, 1 H), 5.20 (s, 1 H); MS (CI) $m/z$ 269 ($MH^+$).

**6B** (fast isomer): $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.28 (t, $J$ = 7.2 Hz, 3 H), 0.90–1.90 (m, 13 H), 2.56 (d, $J$ = 7.2 Hz, 2 H), 3.45 (H3) (dt, $^3J_{2,3}$ = 5.4 Hz and $J$ = 8.3, 9.4 Hz, 1 H), 3.68 (H2) (dt, $^3J_{3,2}$ = 5.4 Hz and $J$ = 6.4 Hz, 1 H), 4.17 (q, $J$ = 7.2 Hz, 2 H), 4.97 (s, 1 H), 5.12 (s, 1 H); MS (CI) $m/z$ 269 ($MH^+$).

**1,1-Dimethylethyl [*S*-(*E*)]-[1-(Cyclohexylmethyl)-4-hydroxy-2-butenyl]carbamate (7).** To a solution of **4** (38.5 g, 0.12 mol)[14] in $CH_2Cl_2$ (280 mL) cooled to −78 °C under $N_2$ was added $BF_3$-$Et_2O$ (17.0 mL, 0.14 mol) and the reaction stirred for 30 min. A solution of DIBAL (254 mL, 0.38 mol, 1.5 N in toluene) was added dropwise followed by stirring for 45 min. The reaction was quenched by slow addition of HOAc/$CH_2Cl_2$ (1:1). After being warmed to rt the solution was evaporated to remove most of the $CH_2Cl_2$ and the remaining gum partitioned between ethyl acetate and 1.0 N aqueous citric acid. The organic layer was separated and washed with 1.0 N citric acid, saturated $NaHCO_3$ solution, and saturated NaCl solution sequentially. After drying ($MgSO_4$) the solution was filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with 3:2 hexane/ethyl acetate to afford **7** (19.14 g, 56%). The product was crystallized from hexane/ethyl acetate to afford white plates: mp 109–112 °C; MS (EI) $m/z$ 284 ($MH^+$); IR (KBr) 3347, 2978, 1702, 1696, 1663 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 0.85–1.90 (m, 14 H), 4.17 (d, $J$ = 6.67 Hz, 2 H), 4.20 (m, 1 H), 4.47 (br d, 1 H), 5.60 (dd, $J$ = 14.7, 6.67 Hz, 1 H), 5.77 (dt, $J$ = 14.7, 6.0 Hz, 1 H). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.74; H, 10.28; N, 4.74.

**1,1-Dimethylethyl [*S*-(*E*)]-[1-(Cyclohexylmethyl)-4-(2,2,2-trichloro-1-iminoethoxy)-2-butenyl]carbamate (8).** To NaH (200 mg, 60% dispersion in mineral oil, 5.0 mmol), washed free of oil with anhydrous THF, in THF (4 mL) at 0 °C, was added alcohol **7** (0.61 g, 2.16 mmol) as a solution in THF (8 mL). The reaction was stirred for 10 min before dropwise addition of trichloroacetonitrile (0.22 mL, 2.16 mmol). After being stirred for 30 min at 0 °C, the reaction was warmed to rt and quenched with $H_2O$ (1 mL). After dilution with ethyl acetate and washing with $H_2O$, the solution was dried ($Na_2SO_4$). Evaporation under reduced pressure afforded a yellow residue which was filtered rapidly through a small pad of silica gel to afford **8** (0.72 g, 97%) as a colored oil; TLC $R_f$ = 0.67 (85:15 hexane/ethyl acetate). No further purification was attempted due to the lability of this compound, and the compound was generally used immediately after preparation: IR (film) 3347, 2977, 2925, 2852, 1701, 1663, 1129 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 0.80–1.40 (m, 7 H), 1.45 (s, 9 H), 1.70 (m, 6 H), 4.25 (br s, 1 H), 4.42 (br s, 1 H), 4.77 (d, $J$ = 3.9 Hz, 2 H), 5.79 (t, $J$ = 4.2 Hz, 2 H), 8.30 (s, 1 H).

**1,1-Dimethylethyl [*S*-(*E*)]-[1-(Cyclohexylmethyl)-2-[(trichloroacetyl)amino]-3-butenyl]carbamate (9). Thermal Overman Rearrangement.** The crude imidate ester **8** (0.60 g, 1.40 mmol) was dissolved in xylenes (bp 137–144 °C) (20 mL) and the solution heated under reflux for 24 h (until all starting material had disappeared by TLC). After the solution was cooled, the solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel eluting with 15% ethyl acetate in petroleum ether to afford the product **9AB** as a 45:55 mixture of inseparable diastereomers (322 mg, 54%): MS(EI) $m/z$ 371 ($M^+$ − $^t$Bu); IR (KBr) 3380, 3006, 2950, 1769, 1694, 1525, 1180 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 4.05 H), 1.45 (s, 4.95 H), 0.90–1.93 (m, 13 H), 3.72 (m, 0.45 H), 4.00 (m, 0.55 H), 4.10–4.56 (m, 2 H), 5.32 (m, 2 H), 5.75 (m, 1 H), 7.95 (br s, 0.45 H), 8.64 (br s, 0.55 H).

**Palladium-Catalyzed Overman Rearrangement.** To the crude imidate ester **8** (283 mg, 0.66 mmol) dissolved in anhydrous THF (5 mL) under $N_2$ was added fresh $Pd(OAc)_2$ (949 mg, 4.22 mmol) and the reaction stirred for 4 h at rt. The crude reaction mixture was evaporated and the residue immediately chromatographed on silica gel eluting with 10–50% ethyl acetate in hexane to afford the product **9A** (127 mg, 45%) as a colorless oil: MS (EI) $m/z$ 371 ($M^+$ − $^t$Bu); IR (KBr) 3380, 3006, 2950, 1769, 1694, 1525, 1180 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 0.90–1.92 (m, 13 H), 4.00 (m, 1 H), 4.22 (br t, 1 H), 4.41 (br s, 1 H), 5.25 (m, 2 H), 5.75 (m, 1 H) 8.68 (br s, 1 H). Anal. Calcd for $C_{18}H_{29}N_2O_3Cl_3$·0.6THF: C, 52.01; H 7.23; N, 5.95; Cl, 22.58. Found: C, 52.15; H, 7.04; N, 6.06; Cl, 23.05.

**1,1-Dimethylethyl (*S*)-[2-Amino-1-(cyclohexylmethyl)-3-butenyl]carbamate (10).** To a solution of **9A** (200 mg, 0.47 mmol) in 95% ethanol (2.5 mL) at rt was added 6 N aqueous NaOH (2.35 mL) and the reaction stirred for 24 h (TLC indicated no starting material remaining). The solution was then diluted with ether (10 mL), ethyl acetate (5 mL), and $H_2O$ (5 mL). The organic layer was separated and the aqueous layer extracted twice more with portions of ethyl acetate (20 mL). The combined organic extracts were washed once with brine and then dried ($Na_2SO_4$). Column chromatography on silica gel eluting with 50 to 100% ethyl acetate/hexane afforded the product **10** as a yellowish oil (103 mg, 78%): MS (EI) $m/z$ 283 ($MH^+$); IR ($CDCl_3$) 3320, 2920, 1700 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) δ 1.10–1.90 (m, 13 H), 1.45 (s, 9 H), 3.42 (m, 1 H), 3.78 (m, 1 H), 4.58 (m, 1 H), 5.18 (m, 2 H), 5.82 (m, 1 H).

**(4*S*-*trans*)-4-(Cyclohexylmethyl)-5-ethenyl-2-imidazolidinone (11).** The amine **10** (130 mg, 0.46 mmol) was dissolved

in a mixture of $CH_2Cl_2$/MeOH (1:1, 10 mL), and anhydrous HCl gas was bubbled through the solution for 15 min. After a further hour of stirring, the solution was evaporated and redissolved in $CHCl_3$ before being washed with saturated $NaHCO_3$ solution and dried ($Na_2SO_4$). After filtration and evaporation under reduced pressure, the resulting diamine was dissolved in toluene (10 mL), and a solution of phosgene (12.5% in toluene, 100 μl) was added. The reaction was stirred for 24 h at rt and then evaporated under reduced pressure in a fume hood. The resulting residue was taken up in ethyl acetate, washed with saturated $NaHCO_3$ solution, and dried ($Na_2SO_4$). The crude product 11 was partially purified by column chromatography on silica gel eluting with $CH_2Cl_2$ to 10% MeOH/$CH_2Cl_2$ to afford a yellowish oil in low yield (20%): $^1$H NMR (250 MHz, $CDCl_3$) δ 0.80–1.80 (m, 13 H), 4.17 (m, 1 H), 4.22 (m, 1 H), 5.38 (m, 2 H), 5.78 (m, 1 H), 7.54 (m, 1 H), 7.71 (m, 1 H).

**Acknowledgment.** We thank Drs. A. MacKeller and G. McClusky and their associates for spectral and analytical data.

**Supplementary Material Available:** $^1$H NMR spectra for compounds **6A**, **6B**, **8**, **9A**, **9AB**, and **10**, $^1$H NMR and IR spectra for compound 8, 250-MHz NOE difference spectra used to establish stereochemistry at C-2 for **6A** and **6B** (Figure 2), a selected region of the 250-MHz $^1$H NMR spectrum of 11 (Figure 3), and plots of the H2–C2–C3–H3 torsion angle for the cis and trans isomers of 11 as a function of time for dynamics calculations at 500 K (Figure 4) (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

# *Additions and Corrections*

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**Yves Queneau,* Walter J. Krol, William G. Bornmann, and Samuel J. Danishefsky.** A Ready Synthesis of Intermediates Containing the A-Ring Substructure of Taxol: A Diels–Alder Route to the B-*seco* Taxane Series.

Page 4044, column 1. The first structure of Scheme III should be drawn as shown: