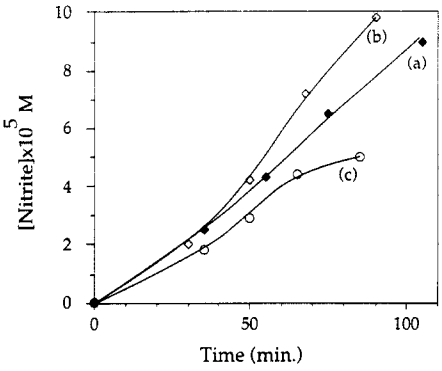

Figure 1. Rate of NO_3^- reduction in the assembly composed of nitrate reductase (0.023 unit, based on native enzyme) immobilized in the acrylamide (**1**) copolymer. In all experiments, $[NO_3^-] = 4.4 \times 10^{-3}$ M in 2.3 mL of Tris buffer, pH = 7.44. (a) Dark reduction in the presence of sodium dithionite, 9.4×10^{-3} M. (b) Through illumination in the presence of $Ru(bpy)_3^{2+}$ (5.5×10^{-5} M) and Na_2EDTA (4.4×10^{-3} M). (c) Through illumination in the presence of $Ru(bpy)_3^{2+}$ (5.5×10^{-5} M), Na_2EDTA (4.4×10^{-3} M), and added MV^{2+} (3.3×10^{-4} M), where the enzyme is immobilized in a nonfunctionalized acrylamide polymer.

Previous studies have shown that reduced methyl viologen, $MV^{\bullet+}$, reduces nitrate to nitrite in a reaction mediated by nitrate reductase.[8,9] In this system, $MV^{\bullet+}$ acts as a diffusing electron carrier to the enzyme's active site. We find that introduction of the **1** functionalized polymer beads that contain immobilized nitrate reductase (0.023 unit, based on native enzyme) to an aqueous solution, pH = 7.44, that includes nitrate, 4.4×10^{-3} M, and dithionite, 9.4×10^{-3} M, results in the formation of nitrite (Figure 1a). Similarly, illumination ($\lambda > 400$ nm) of a photosystem consisting of the enzyme (0.023 unit) immobilized in the functionalized polymer in an aqueous solution, pH = 7.44, $Ru(bpy)_3^{2+}$ (5.5×10^{-5} M), and $EDTANa_2$ (4.4×10^{-3} M) results in the reduction of nitrate to nitrite (Figure 1b). During both photochemical and chemical reduction reactions, the polymer appears dark blue (a color characteristic of 4,4'-bipyridinium radicals). All the components in the system are essential for the reduction (or photoreduction) of NO_3^-. Thus no nitrite is formed either in the absence of added nitrate or upon exclusion of the enzyme. Also, the reduction of NO_3^- is not directly affected by dithionite, and no formation of NO_2^- is observed when dithionite is added to nitrate reductase immobilized in a polyacrylamide polymer that is bare of the **1** copolymer. The results indicate that the polymer-anchored bipyridinium radical, formed by reduction of dithionite or through photochemical means, reduces the polymer-immobilized enzyme. We also observe that the rates of NO_2^- formation are similar for dithionite and the photosystem, and that MV^{2+} added to a nonfunctionalized acrylamide polymer that includes the biocatalyst, decreases slightly the rate of NO_3^- reduction, Figure 1c. These results suggest that the rate of NO_3^- reduction is limited by the process occurring at the biocatalyst active site. Laser flash photolysis experiments[10] in a photosystem composed of $Ru(bpy)_3^{2+}$ and polymer-immobilized nitrate reductase allow us to determine the electron-transfer rate constant, k_{et}, from the photoreduced polymer to the biocatalyst active site. The estimated value of this rate constant is $k_{et} = (9 \pm 3) \times 10^5$ s^{-1}.

A functional polymer–biocatalyst organization does not always result in an active assembly. Similar immobilization of glutathione reductase does not lead to an electron-transferring system, despite the fact that $MV^{\bullet+}$ does act as a diffusing electron carrier to this enzyme.[10] The lack of activity of glutathione reductase in the functionalized polymer is attributed to the protein crowded environment of the enzyme active site, which prevents direct electron-transfer communication with the polymer.

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(10) Lapidot, N., unpublished results.

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Registry No. **1**, 128269-89-6; **2**, 128269-88-5; **3**, 38862-24-7; NO_3^-, 14797-55-8; nitrate reductase, 9013-03-0; acrylamide, 79-06-1; *N,N'*-methylenebis(acrylamide), 110-26-9; 4,4'-bipyridine, 553-26-4; *N*-(*tert*-butoxycarbonyl)-3-amino-1-bromopropane, 128412-15-7.

Synthesis of the Ketodifluoromethylene Dipeptide Isostere

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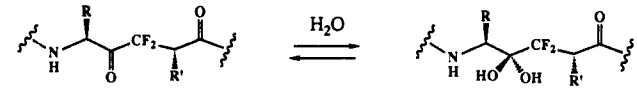
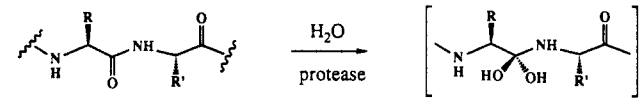
Received May 7, 1990

The inhibition of aspartic proteases such as human renin and HIV protease is a pressing problem in bioorganic chemistry. In this paper we present a solution to a critical element of this problem, the synthesis of the ketodifluoromethylene dipeptide isostere (I). This structure as the hydrate closely resembles II,

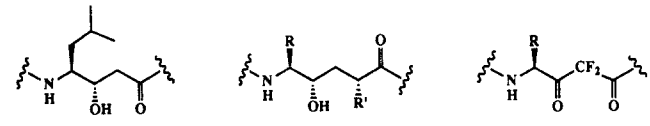


I, Ketodifluoromethylene Dipeptide Isostere



Protease Substrate II, Tetrahedral Intermediate

the putative tetrahedral intermediate in proteolytic cleavage of the peptide bond, differing only in substitution of difluoromethylene for tetrahedral nitrogen. Our interest in the synthesis of I has been driven by the vital contributions of more distant mimics of intermediate II, namely, statine and its derivatives,[1,2]



Statine Hydroxyethylene Dipeptide Isostere Difluorostatone

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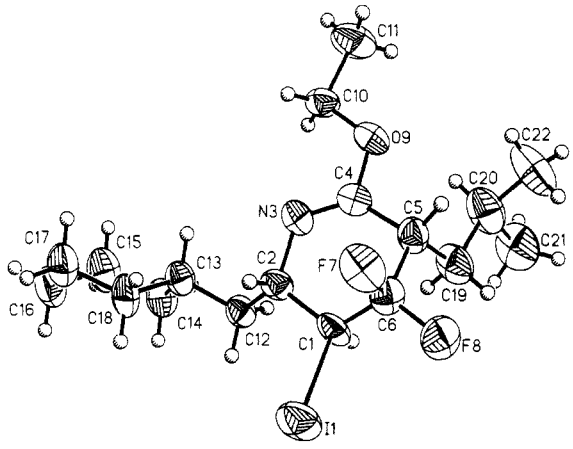
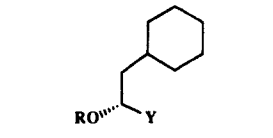
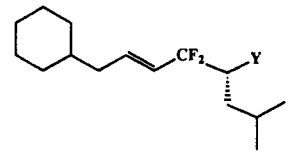


Figure 1. Molecular structure and labeling scheme for (±)-**8** (50% thermal ellipsoids).

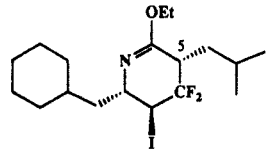
the hydroxyethylene dipeptide isosteres,[3] and the readily hydrated difluorostatones,[4] to the inhibition and mechanistic study of the aspartic proteases.[5,6] This report should stimulate the synthesis of a new class of enzyme inhibitors and especially useful probes (via X-ray crystallography and NMR) of the mechanism and active-site geometry of hydrolytic enzymes.[7] Methodology is illustrated for the example possessing R = cyclohexylmethyl and R′ = isobutyl substituents.[8] The requisite difluorinated carbon skeleton was constructed by silylketene acetal Claisen rearrangement of the allylic ester **4**, obtained from methyl (*R*)-phenyllactate[9] by the following sequence (each intermediate purified by distillation from $CaCO_3$): (1) catalytic reduction (10% Rh–C, CH_3OH–HOAc, 92%) to **1**;[10] (2) silylation of **1** with 1.05 equiv of TMS–CN at 20 °C (98%); (3) reduction of the silyloxy ester with 2.2 equiv of diisobutylaluminum hydride in hexane and quenching with excess MeOH at ≤−70 °C followed by addition of Rochelle salt solution and extraction to give **2** (94%); (4) difluoromethylenation[11] by addition of **2** at 25 °C to the solution resulting from treatment of 1.9 equiv of CF_2Br_2 in THF with 3.5 equiv of HMPT at ≤−65 °C and chromatography to give the difluorinated allylic ether (65%); (5) desilylation with NaOH in MeOH–H_2O to give **3** of at least 94% enantiomeric purity[12] (94%); and (6) esterification by sequential treatment with 1.05 equiv of *n*-BuLi and 1.1 equiv of 4-methylvaleryl chloride in hexane at −78 °C to give **4** in 84% yield.



1, R = H, Y = CO_2Me
2, R = TMS, Y = CHO
3, R = H, Y = $CH{=}CF_2$
4, R = $C(O)CH_2i$-Bu, Y = $CH{=}CF_2$



5, Y = COOH
6, Y = $CONH_2$
7, Y = C(OEt)=NH



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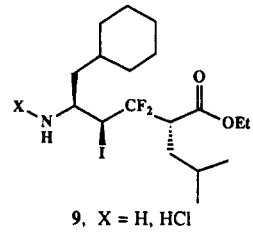
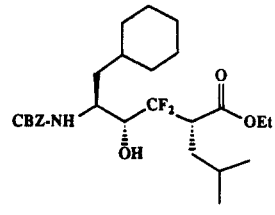


9, X = H, HCl
10, X = CBZ



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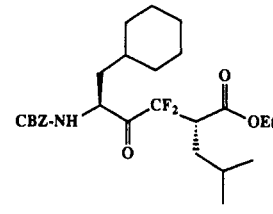

12

Enolization of **4** with 1.18 equiv of $LiN(TMS)_2$ in THF at −90 °C for 10 min, sequential addition of HMPA (3 equiv) and 1.2 equiv of *tert*-butyldimethylsilyl chloride in THF (−90 °C for 10 min, −78 °C for 20 min, 25 °C for 2 h) and hydrolysis (10 equiv of 2 N HCl, 16 h, 25 °C) gave **5** [absolute configuration established by the (*S*)-1-phenethylamide X-ray structure] of 88% en-

(3) See ref 1k and: (a) Szelke, M.; Jones, D. M.; Atrash, B.; Hallett, A.; Leckie, B. In *Peptides: Structure and Function. Proceedings of the 8th American Peptide Symposium*; Hruby, V. J., Rich, D. H., Eds.; Pierce Chemical Co.: Rockford, IL, 1983; pp 579–582. (b) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374–383. (c) Kati, W. M.; Pals, D. T.; Thaisrivongs, S. *Biochemistry* **1987**, *26*, 7621–7626. (d) DeGasparo, M.; Cumin, F.; Nussberger, J.; Guyenne, T.; Wood, J. M.; Menard, J. *Br. J. Clin. Pharmacol.* **1989**, *27*, 587–596. (e) McQuade, T. J.; Tomasselli, A. G.; Liu, L.; Karacostas, V.; Moss, B.; Sawyer, T. K.; Heinrikson, R. L.; Tarpley, W. G. *Science* **1990**, *247*, 454–456. (f) Murphy, W. R.; MacAndrew, J. T.; Kleinman, E. F.; Holt, W. F. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 845. Mento, P. F.; Holt, W. F.; Murphy, W. R.; Wilkes, B. M. *Hypertension* **1989**, *13*, 741–748.

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(10) Satisfactory elemental analytical and/or high-resolution mass and ^1H, ^{13}C, and (as appropriate) ^{19}F NMR spectral data were obtained for each new substance reported herein. Unless otherwise specified yields refer to material carried forward in the next step after having been purified by chromatography and found homogeneous by 75-MHz ^{13}C NMR.

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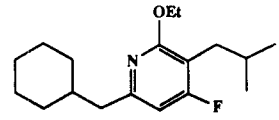
(12) One olefinic resonance was observed by ^1H NMR in a concentrated benzene-d_6 solution of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (cf. p 276 in Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263–331) where the racemate gives a well-resolved additional resonance (arising from (*S*)-**3**).

antiomeric purity[13] in 80–90% yield.[14] These conditions thus effect *E* enolization of **4** if the silylketene acetal is rearranging via the expected chair transition state.[15] *Remarkably, this rearrangement did not occur when* **4** *was exposed to LDA at −78 °C under these conditions.*[16] Reaction of **5** with 10 equiv of $(COCl)_2$ and a trace of DMF[17] in toluene at 25 °C gave the crude acid chloride, which was treated with excess NH_3 in dichloromethane at 0 °C giving amide **6** in 75% yield after recrystallization from hexane, $[\alpha]^{23}_D$ +10.7° (*c* = 1.0, $CHCl_3$). *O*-Alkylation with 1.35 equiv of Et_3OBF_4[18] in dichloromethane (25 °C, 24 h) produced imino ester **7** (95%).

Preliminary studies on the halolactonization of acid **5**[19] directed us to explore the iodocyclization of imino ester **7**[20] as a means of initiating regiospecific double bond oxyamination which could result in the proper stereochemical relationships of the target isostere I. After some experimentation, reaction of a mixture of **7**, 1.4 equiv of iodine, 10 equiv of $NaHCO_3$, and 0.02 equiv of 4,4′-thiobis(2-*tert*-butyl-6-methylphenol) (TBP) in 1:1 dichloromethane–H_2O in the dark at 25 °C for 24 h gave, after ethyl acetate–aqueous thiosulfate extraction and rapid filtration through silica gel (eluted with 0.25:2:100 ether–triethylamine–hexane), an 11:1 mixture of cyclic imidate **8** and another CF_2-containing substance presumed to be the expected diastereomer in 83% yield.[21,22] The conversion of **8** to the monofluoropyridine **13** during purification and handling was suppressed by added triethylamine.



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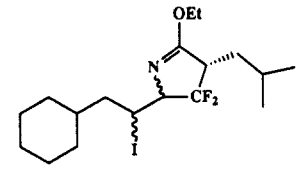

14

The X-ray structure of (±)-**8**[23] (Figure 1) suggests a transition state with similarly disposed substituents minimizing both $A^{1,2}$ strain[24] between the isobutyl and ethoxyl groups as well as the pseudo-1,3-diaxial interactions of the iodine and cyclohexylmethyl ligands. *In the absence of TBP in ambient light,* **7** reacted with iodine under these conditions to produce predominantly four isomeric pyrrolines **14**, by a more rapid, presumably radical process. Hydrolysis of (±)-**8**[25] at 0 °C[26] with 2.2 equiv of HCl in 2:1 THF–H_2O produced acyclic hydrochloride **9**, which was crystallized from dichloromethane–ether in 44–68% yield (unoptimized) and converted to the benzyl carbamate **10** (5 equiv of CBZ-Cl, 1:1 THF–saturated aqueous $NaHCO_3$, 0 °C, 87%). Iodide **10** underwent facile stereospecific hydrolysis to the protected amino alcohol **11** under neutral conditions upon exposure to 10 equiv of buffered peroxytrifluoroacetic acid[27] in dichloromethane at 0 °C (73% yield). The stereochemistry of **11** was determined by X-ray analysis. This novel transformation occurred as well on the analogous Boc (80%) and trichloroacetyl (>90%) derivatives, presumably by intramolecular carbamate-assisted displacement of hypervalent iodine.[28] In contrast, attempts to effect hydrolysis of iodide **10** by silver or mercuric ion were unsuccessful and base-catalyzed oxazoline formation could not be accomplished without HF elimination. Modified Pfitzner–Moffatt oxidation[29] of **11** with 6 equiv of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride and 0.6 equiv of dichloroacetic acid in 1:1 toluene–DMSO at 25 °C produced the target fluoro ketone **12** in 78% yield. These results set the stage for the synthesis and study of new peptide enzyme inhibitors bearing isostere I, which will be reported in due course.

Acknowledgment. We are grateful to Professor E. J. Corey, J. R. Hauske, Bernard Hulin, Bruce A. Lefker, Professor Stuart L. Schreiber, and Professor Dieter Seebach for helpful discussion and comment, and to Alex Grodski and Mark L. Elliott for preparing (±)-**3**. We are also deeply indebted to Jon Bordner and Debbie DeCosta for the X-ray structures, Earl B. Whipple, Stephen C. Maginess, and Diane M. Rescek for numerous definitive NMR spectra, and to Jeffrey P. Kiplinger, Daniel T. Pentek (Yale University Chemical Instrumentation Center), and Richard S. Ware for mass spectra. We thank also Lawrence S. Melvin and Rodney C. Schnur for critical review of the manuscript, Robert A. Volkmann for strategic advice, and John L. LaMattina for his encouragement and support.

Supplementary Material Available: Complete experimental details for the procedures discussed, spectral properties (including

(13) By HPLC analysis of the corresponding 3,5-dimethylanilide in 10% 2-propanol–hexane on the chiral stationary phase described by Pirkle and McCune: Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1988**, *441*, 311–322. We thank Professor Pirkle for providing this column and for helpful comments regarding the resolution.

(14) For orthoester Claisen rearrangement of related fluorine-containing substrates see: (a) Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron Lett.* **1985**, *26*, 2861–2864. (b) Taguchi, T.; Morikawa, T.; Kitagawa, O.; Mishima, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5137–5140. (c) The silylketene acetal Claisen rearrangement of a related nonfluorinated substrate has been employed in the synthesis of a hydroxyethylene dipeptide isostere: Herold, P.; Dothaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178–1185.

(15) See ref 15 in: Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479–485.

(16) Related reactivity phenomena of LDA-derived enolates have been discussed and the use of $LiN(TMS)_2$ in avoiding such complications suggested: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654. Seebach, D. Presented at the Corey Symposium, Harvard University, November 5, 1988. The conditions described by Ireland et al. (Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877) for the preparation of their compound **2h** were employed, except that LDA was generated in THF–hexane. **4** was recovered in high yield together with 10–20% of **3**. In contrast, analogous *non*fluorinated substrates rearrange in near-quantitative yield under these conditions (Hoover, D. J.; Eberhardt, E. S., unpublished observations). No deuterium incorporation in **4** is detectable (<5%; FAB-MS) after CD_3COOD quenching of LDA-treated **4** at −78 °C (e.g., **4**, THF, LDA, 5 min; HMPA, 1 min; HOAc-d_4, all at −78 °C).

(17) (a) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972–3974. (b) Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. *Synthesis* **1976**, 767–768.

(18) *Organic Syntheses*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, pp 1080–1082.

(19) Cyclization of **5** to mixtures of six-membered halolactones occurred on exposure at 25 °C to NBS in DMF (2:1 mixture, 72%) or I_2–aqueous $NaHCO_3$ (8:1, 80%), the major isomer in each case corresponding in stereochemistry to **8** (NMR assignments).

(20) Iodocyclization of *N,O*-bis(trimethylsilyl)imino esters to lactams is reported: Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803–1806.

(21) **8** was homogeneous (thus >90% ee) by ^{19}F NMR in a concentrated benzene-d_6 solution of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (see ref 12) where nonequivalence between the less shielded fluorine nuclei of the enantiomers is observed in the racemate.

(22) The rate of cyclization of **7** to **8** under these two-phase aqueous conditions using halogenated cosolvents decreased in the following order: $(ClCH_2)_2 = CH_2Cl_2 > CHCl_3 > CCl_4$. Little conversion occurred when THF or MeCN was employed. We note with some interest that **8** could also be produced in 75–80% yield under nonaqueous conditions (to 25-mmol scale) after reaction of a *sonicated* (Bransonic 221 laboratory ultrasonic cleaner, 185 W) mixture of **7**, 2 equiv of iodine, and 6 equiv of $NaHCO_3$ in 1:1 THF–MeCN for 24 h at 40 °C. No radical inhibitor was added, though the apparatus was usually covered to prevent evaporation of the bath and thus darkened to some extent. Under these conditions little or no pyrrolines **14** formed, and 10% of a single C-5 hydroxylated derivative of **8** was also isolated. In contrast, **7** was recovered essentially unchanged when stirred with TBP in the dark in analogous fashion. Sonication thus accelerates this cyclization, and under these conditions the radical process is suppressed.

(23) The enantiomerically pure material **8** was an oil. (±)-**8** was derived from (±)-**3** obtained from the −100 °C condensation of 2,2-difluorovinyllithium (Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 957–958) with 1.0 equiv of cyclohexylacetaldehyde in 5:1 THF–ether.

(24) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.

(25) The subsequent reactions were characterized on racemates derived from (±)-**3**. The products **9–12** and **14** are shown for convenience in the enantiomeric form corresponding to I.

(26) Hydrolysis of **8** at 25 °C produced **13** as a substantial byproduct.

(27) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 89–92.

(28) An analogous transformation in vicinal iodocarbonates is reported: Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc. Perkin Trans. 1* **1980**, 822–827.

(29) See ref 4c and: Pfitzner, K. E.; Moffat, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661–5670.

high-field ^1H, ^{13}C, ^{19}F NMR) of the products, and tables of positional and thermal X-ray parameters for (±)-**8**, **11**, and the (*S*)-1-phenethylamide of **5** (34 pages).[30] Ordering information is given on any current masthead page.

(30) X-ray crystal data were collected on a Nicolet R3m/μ diffractometer: λ = 1.5418 Å, T = 298 K, θ–2θ scan mode, 5° ≤ 2θ ≤ 100°. For (±)-**8** (from hexanes): $C_{18}H_{30}NOF_2I$, 0.19 × 0.20 × 0.23 mm, $P\bar{1}$, Z = 2, a = 9.516 (3) Å, b = 10.425 (4) Å, c = 12.063 (6) Å, α = 108.09 (3)°, β = 98.03 (4)°, γ = 112.89 (3)°, V = 1000.5 (7) Å^3, D_{calcd} = 1.46 g/cm^3. A total of 2011 unique reflections were measured; 1811 were considered observed [$I > 3.0\sigma(I)$] and were used in subsequent structure analysis, yielding R = 0.066, R_w = 0.067, and GOF = 1.79. For **11** (from hexanes): $C_{26}H_{39}NO_5F_2$, 0.18 × 0.36 × 0.52 mm, $P2_1/n$, Z = 4, a = 15.912 (3) Å, b = 9.710 (3) Å, c = 18.298 (6) Å, β = 105.94 (2)°, V = 2718 (1) Å^3, D_{calcd} = 1.18 g/cm^3. A total of 2777 unique reflections were measured; 2300 were considered observed [$I > 3.0\sigma(I)$] and were used in the subsequent structure analysis, yielding R = 0.059, R_w = 0.067, and GOF = 1.62. A difference map revealed that the ester ethyl group was disordered; this disorder was fit by using two positions for the ethyl group (3:1 population). The hydrogens for this disordered group were not located. For the (*S*)-1-phenethylamide of **5** (from methanol): $C_{24}H_{35}NOF_2$, 0.13 × 0.21 × 0.34 mm, $P2_1$, Z = 4, a = 9.737 (2) Å, b = 10.540 (3) Å, c = 23.068 (7) Å, β = 90.49 (2)°, V = 2367 (1) Å^3, D_{calcd} = 1.10 g/cm^3. A total of 2599 unique reflections were measured; 2168 were considered observed [$I > 3.0\sigma(I)$] and were used in the subsequent structure analysis, yielding R = 0.061, R_w = 0.063, and GOF = 1.01.

Synthetic Studies on Transition-Metal-Mediated Higher Order Cycloaddition Reactions: Highly Stereoselective Construction of Substituted Bicyclo[4.4.1]undecane Systems

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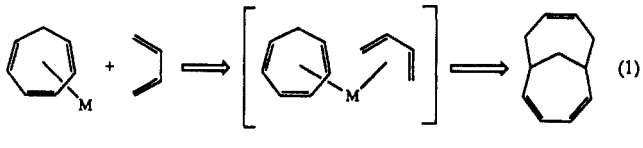
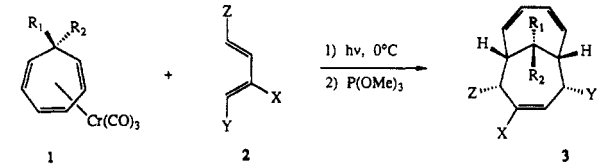
So called higher order cycloaddition reactions ($6\pi + 4\pi$, $4\pi + 4\pi$, $6\pi + 2\pi$) are typically characterized by a high level of stereoselectivity and relatively low chemical efficiency. Tropone, for example, participates in a thermally allowed [6 + 4] cycloaddition with a limited range of dienes to provide adducts in modest yields with extremely high exo stereoselectivity.[1] Cycloheptatriene on the other hand, displays little periselectivity in thermal reactions with dienes, giving a myriad of products of which the [6 + 4] adduct is only a minor component.[2] The notion of employing a transition-metal template to enhance the efficiency of the higher order process by rendering the reaction temporarily intramolecular is quite appealing. Surprisingly, this strategy has received relatively little attention in the realm of higher order cycloaddition chemistry.[3] In the present case, it was envisioned that an appropriate metal could serve to precomplex both the 6π and 4π addends, thus providing an opportunity for promoting the desired pathway as depicted in eq 1.



(1)

In the formative stages of this study, we were intrigued by reports from the Kreiter laboratory of a photochemical ligand exchange involving several cyclic triene–chromium complexes that produced the desired bicycle stereoselectively in simple cases.[4] In light of the significant potential for rapid assembly of highly substituted systems exhibiting substantial stereochemical information, we elected to explore the photochemical behavior of variously 7-substituted tricarbonyl-η-1,3,5-cycloheptatriene–chromium complexes with representative dienes. We report that transition-metal-mediated cycloadditions can effectively produce highly functionalized bicycles stereoselectively with none of the limitations that often plague the thermal versions. The results of this work are compiled in Table I. Typically, the reactions in this study were performed by irradiating a solution of the triene chromium tricarbonyl complex and diene partner at 280 nm at 0–5 °C for several hours, followed by decomplexation with trimethyl phosphite to give the organic product.

Table I. [6 + 4] Cycloaddition of Tricarbonyl-η-1,3,5-cycloheptatriene Chromium



1 2 3

entry	triene **1**	diene **2**	yield,[a,b] %
1	R_1, R_2 = H	X, Y = H; Z = OMe	64
2	R_1, R_2 = H	X, Y = H; Z = OTMS	56
3	R_1, R_2 = H	X, Y = H; Z = OAc	67
4	R_1, R_2 = H	X = H; Y, Z = OAc	65
5	R_1, R_2 = H	X = H; Y, Z = CO_2Me	59
6	R_1 = H; R_2 = OMe	Y, Z = H, X = Me	66
7	R_1 = OMe; R_2 = H	Y, Z = H; X = Me	60
8	R_1 = OMe; R_2 = H	X, Y = H; Z = OAc	60
9	R_1 = Me; R_2 = H	X, Y = H; Z = OMe	47
10	R_1 = Me; R_2 = H	X = H; Y = CO_2Me; Z = Me	59
11	R_1, R_2 = H	Y, Z = H; X = OTMS	82[c,d]
12	R_1, R_2 = OMe	Y, Z = H; X = Me	67[e]

[a] All products described in this table are purified and exhibit spectral (^1H NMR, ^{13}C NMR, IR) and analytical (HRMS and combustion analysis) data consistent with the assigned structures. [b] Yields are reported for isolated and purified adducts after metal decomplexation. [c] Yield is for combined TMS enol ether and ketone products. [d] Intermediate observed in this entry was not isolated. [e] This compound was correlated with the corresponding cycloadduct derived from tropone.

Examination of Table I reveals a number of noteworthy features of this reaction. Of particular importance is the observation that the efficiency of the transformation appears to be independent of the electronic nature of the diene. Thus, both electron-rich partners (entries 1–4, 8, 9, and 11) and electron-deficient dienes (entries 5 and 10) participate smoothly. The comparable yields obtained for the reactions of 1,4-diacetoxybutadiene (entry 4) and dimethyl muconate (entry 5) are particularly dramatic illustrations of this point. The ability to effect this cycloaddition with either exo or endo 7-substituted cycloheptatriene complexes,[5] both of which are readily available with numerous subtituents, makes this a powerful method for producing adducts possessing considerable stereochemical information. Indeed, as many as five contiguous stereogenic centers can be created in one step, using this protocol (entries 8–10). Exploitation of the well-known facial bias that prevails in the resultant bicyclic systems to install additional substituents in a stereocontrolled fashion around the periphery of the ring is an additional advantage of this methodology.[1d] A remarkable result was obtained when 2-[(trimethylsilyl)oxy]butadiene was employed as the diene addend (entry 11). In this case, the expected bicyclo[4.4.1]undecane complex was not produced during the photochemical step. Instead, an unstable and structurally ill-defined intermediate was obtained, which could be induced to collapse efficiently to the desired complex by stirring

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(2) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4143.

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