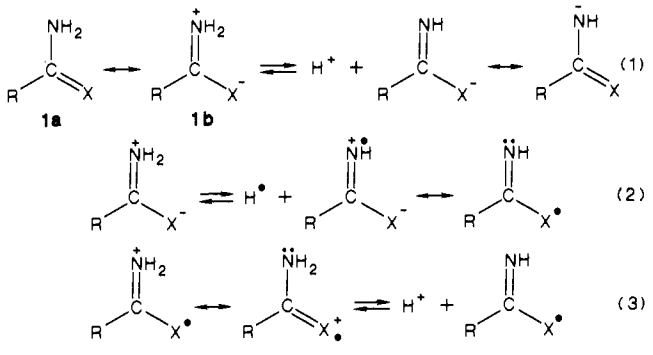
Table I. Acidities of Carboxamides and Thiocarboxamides and of the Radical Cations Derived Therefrom in Me_2SO at 25 °C

amide	pK_{HA}	$E_{ox}(A^-)^e$	$E_{ox}(HA)^f$	BDE[g]	$pK_{HA}^{\bullet+}$ [h]
CH_3CONH_2	25.5[a]	+0.725 (110)	+3.286 (250)	107.5	-18
CH_3CSNH_2	18.5[b]	+0.434 (110)	+1.212 (140)	91	+5
$CH_3CONHPh$	21.45[a,c]	+0.605 (70)	+2.140 (160)	99.5	-5
$CH_3CSNHPh$	14.7[b,d]	+0.670 (150)	+1.150 (120)	91.5	+7
$PhCONH_2$	23.35[a]	+0.824 (160)	+2.844 (120)	107	-11
$PhCSNH_2$	16.9[b]	+0.499 (70)	+1.157 (90)	90.5	+6
$(H_2N)_2C{=}O$	26.9[a]	+0.788 (170)	+3.104 (230)	111	-12
$(H_2N)_2C{=}S$	21.0[b]	+0.361 (110)	+1.074 (160)	93	+5
$(PhNH)_2C{=}O$	19.5[b]	+0.425 (70)	+1.951 (60)	92.5	-6
$(PhNH)_2C{=}S$	13.5[b]	+0.561 (50)	+1.117 (60)	87	+4

[a] Reference 1. [b] Algrim, D. J. Ph.D. Dissertation, Northwestern University, 1981. [c] pK_{HA} = 13.8 in H_2O (ref 2). [d] pK_{HA} = 11.6 in H_2O (ref 2). [e] Measured in Me_2SO (V) versus a Ag/AgI electrode by cyclic voltammetry (CV) by using the method described previously[3] and referenced to the standard hydrogen electrode (SHE_{aq}); wave widths in mV are given in parentheses. [f] Measured in MeCN (V) by CV and referenced to SHE_{aq}. [g] Estimated by using the following equation:[4,5] BDE (kcal/mol) = $1.37pK_{HA} + 23.06E_{ox}(A^-) + 55.86$. [h] Estimated to be accurate to about ±2 units by using the equation $pK_{HA}^{\bullet+} = pK_{HA} + [E_{ox}(A^-) - E_{ox}(HA)]23.06/1.37$.[9]

PhNHC(=X)NHPh, the ΔpK_{HA} values remain about the same (9.3 and 8.2 kcal/mol), but the ΔBDE values are decreased sharply (8.0 and 5.5 kcal/mol), as are the $\Delta pK_{HA}^{\bullet+}$ values (16 and 14 kcal/mol).

The large differences in the properties of carboxamides and their thio analogues can be rationalized in part by the superior ability of sulfur, relative to oxygen, in stabilizing $RC(=X)NH^-$ anions (eq 1), $RC(=NH)X^\bullet$ radicals (eq 2), and $RC(=X)NH_2^{+\bullet}$ radical cations (eq 3).



When X in eq 1 and 2 is changed from O to S, the equilibria shift to the right because of the superior ability of sulfur in stabilizing the negative charge or odd electron, but in eq 3 the equilibrium shifts to the left (Table I) because the stabilizing effect of S versus O is greater on the radical cation than on the radical.

The inherent greater ability of sulfur than oxygen to accommodate a negative charge is suggested by the greater acidity of PhSH than PhOH by 10.7 kcal/mol in Me_2SO and 8.5 kcal/mol in the gas phase, which can be explained by a decrease in lone pair–lone pair interactions in the larger S^- ion.[12a] An adjacent PhS function is also far more effective in stabilizing a carbanion than is a PhO function.[12b] There is qualitative evidence that PhS• radicals are more stable than PhO• radicals, and there is ESR data to indicate that RS functions are better than RO functions at stabilizing either adjacent[13] or para[14] carbon-centered radicals. Finally, in gas phase, there is evidence that MeS is superior to MeO in stabilizing the positive charge in $MeXCH_2^+$ cations.[15] The superiority of sulfur over oxygen in these respects is greatly exaggerated in thiocarboxamides versus carboxamides because the C=S bond is weaker than the C=O bond by about 30 kcal/mol,[16] which increases the contribution of **1b**, relative to **1a**, more for X = S than for X = O. For the thioamides this leads to IR stretching frequencies for CN typical of C=N, to CS IR frequencies normally associated with C-S, to higher C=N rotational barriers (15.4 versus 7.5 kcal/mol), and to higher dipole moments.[2]

Replacement of a hydrogen atom on nitrogen by a phenyl substituent has about an equal effect in increasing the acidities of the carboxamides and thiocarboxamides, probably because the negative charge in the anions is localized primarily on oxygen or sulfur, and delocalization of the charge to nitrogen is encouraged to about an equal degree by phenyl substitution. On the other hand, phenyl substitution has a much greater effect in lowering the BDE of the N-H bond in carboxamides and in decreasing the acidities of the radical cations derived therefrom than for the thiocarboxamides, probably because the radicals (eq 2) and radical cations (eq 3) for X = S are already effectively stabilized by localization of the odd electron and positive charge on the sulfur atom but less so for the oxygen atom where X = O.

Acknowledgment. We are grateful to the National Science Foundation for support of this research.

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Nickel-Catalyzed Intramolecular [4 + 4] Cycloadditions. 4. Enantioselective Total Synthesis of (+)-Asteriscanolide

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We recently reported the development of methodology, based on nickel-catalyzed intramolecular [4 + 4] cycloadditions of unactivated bis-dienes, which provides practical access to fused and bridged ring systems incorporating eight-membered carbocycles.[1] Described herein is the application of this methodology to the first synthesis of the recently characterized sesquiterpene lactone (+)-asteriscanolide (**1**).[2] This study establishes the first asymmetric synthesis of a cyclooctane-containing terpenoid[3] and

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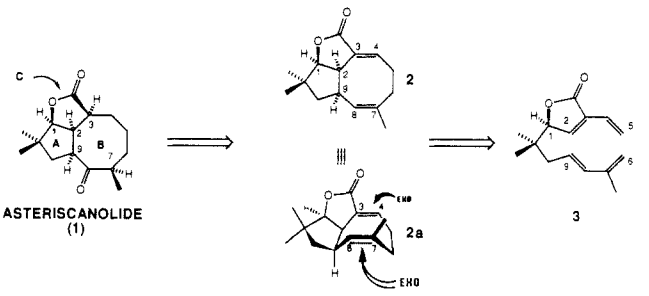
Scheme I



is based on the highest enantioselectivity yet reported for a Darvon alcohol modified lithium aluminum hydride reduction of a propargyl ketone.[4] This combination of methodology for cyclooctane construction and for asymmetric control provides a concise and highly stereocontrolled route to the new asteriscane skeletal class and serves more generally to establish the basis for the broad implementation of this chemistry in synthesis.

Our synthetic plan for asteriscanolide rested, in part, on the expectation that its C3 and C7 stereocenters could be set by selective delivery of hydrogen to the less-hindered exo face of the C3,C4 and C7,C8 double bonds in precursors such as **2** (Scheme I). Since the basis for this facial selectivity is attributable to the conformational constraints and steric effects imparted by the C1, C2, and C9 stereogenic centers, the overall success of this plan would ultimately be determined by the stereochemical outcome of the cycloaddition of bis-diene **3**. Favoring the desired outcome in this key process would be the preference for the development of the less strained cis fusions in the AB and AC ring systems.

The execution of this plan began with the addition of isopropenyl lithium to acrolein (Scheme II). The resulting alcohol **4**[5] was parlayed into the diene acid **5** by esterification with isobutyric anhydride followed by a regio- and stereoselective enolate Claisen rearrangement.[6,7] The direct conversion of the carboxylic acid functionality in **5** to an aldehyde proved problematic, so a two-step procedure involving LAH reduction and Swern[8] oxidation was used. Subsequent addition of lithium vinylacetylide to the resulting aldehyde provided racemic **6** in high yield.

While (±)-**6** was expected to serve in our studies toward racemic asteriscanolide, it was anticipated that an asymmetric synthesis could be fashioned at this point through conversion of this racemic material to ***R*-6**, a procedure which more generally could prove useful in future applications of nickel-catalyzed bis-diene cyclizations. Toward this end, (±)-**6** was oxidized under Swern's conditions,[8] and the resulting *tert*-alkyl alkynyl ketone was submitted to asymmetric reduction. Amongst the reagents examined, the Darvon alcohol modified LAH reagent[4] proved superior, providing ***R*-6** in exceptional chemical (95%) and optical yield (>98% ee).[9]

The next phase of our strategy called for the conversion of propargyl alcohol ***R*-6** to butenolide **3**. While similar transformations have been achieved in related systems via the Pd-catalyzed carbonylation of vinyl iodides,[10] this procedure gave **3** but only in low yield, due largely to the instability of the vinyl iodide intermediate. Consequently, an alternative procedure for accomplishing this transformation was explored. Hydroalumination of the alkyne in ***R*-6** was accomplished in a stereo-, regio-, and chemoselective manner with Red-Al, and the resulting vinylaluminate was stannylated at −78 °C with Me_3SnCl.[11] This resulted in a mixture of products including the expected vinyltin compound **7** and the 1,3-rearranged isomers **8a,b**. The extent of rearrangement and therefore the ratio of products varied with reaction time. Related stannyl migrations have been reported for simple 3-stannyl-1,3-diene/1-stannyl-2,3-diene systems on treatment with strong nucleophiles (e.g., MeLi, Me_3SnLi) at room temperature[12] or under free-radical conditions[13] with the thermodynamic product typically being the 3-stannyl isomer. In our system, however, the rearrangement occurs at −78 °C since at low conversions the 3-stannyl isomer **7** was found to predominate, whereas the 1-stannyl isomers **8a,b** were favored on extended reaction time. From a synthetic standpoint the formation of this mixture of products was not problematic since it was shown that each purified isomer or the mixture can be metalated on treatment with *n*-butyllithium and that the resulting lithium reagent is carboxylated at the internal position to provide, on acidic workup, the desired lactone **3**.

The availability of bis-diene **3** through the above nine-step sequence set the stage for the investigation of the key nickel-catalyzed cycloaddition. This substrate incorporates three features not previously studied in the nickel-catalyzed intramolecular cycloaddition reactions, namely substituents on both dienes, an electron-withdrawing group at the internal position of one diene, and the inclusion of one olefin in a pre-existing ring. Gratifyingly, these features did not frustrate the intended process; the cyclization proceeded quite well, with excellent mode-[14] and stereoselectivity, providing **2** in 67% yield. Completion of the synthesis from **2** then proceeded according to plan. Thus, conjugate reduction of the unsaturated lactone with copper hydride[15] and selective kinetic protonation of the resulting enolate from the exo face produced **9** in greater than 95% isomeric purity. Finally, the C7 stereocenter was established through exo face hydroboration; in situ chromium oxidation of the resultant borane[16] introduced the C6 ketone, directly furnishing (+)-asteriscanolide (**1**).[17]

In summary, a short, enantioselective synthesis of (+)-asteriscanolide based on the nickel-catalyzed intramolecular [4 + 4] cycloaddition reaction has been developed, proceeding in 13 steps and 2.7% overall yield. This study also provides general protocols for the facile construction of bis-dienes and for the incorporation of enantiocontrol into the synthetic strategy. Further applications

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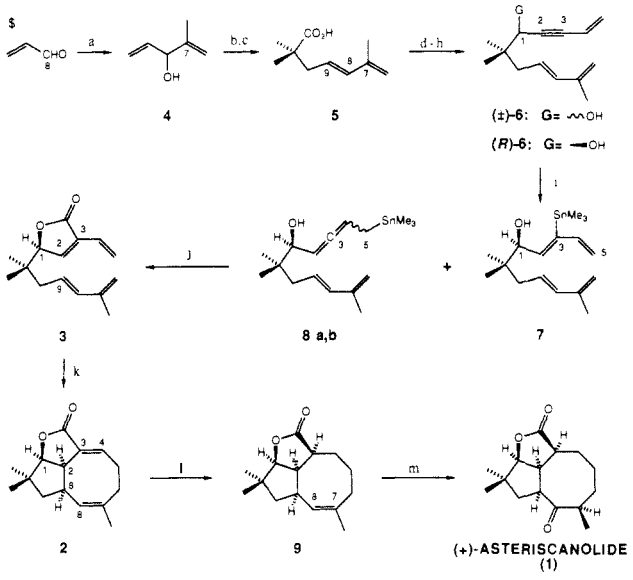
Scheme II[a]



[a] (a) Isopropenyl Grignard (57%); (b) isobutyric anhydride (99%); (c) LDA, -78 °C to 0 °C (69%); (d) LAH (93%); (e) DMSO, $(COCl)_2$, Et_3N (88%); (f) $LiC{\equiv}CCH{=}CH_2$ (88%); (g) DMSO, $(COCl)_2$, Et_3N (89%); (h) LAH/Darvon (97%); (i) Red-Al; Me_3SnCl (83%); (j) *n*-BuLi; CO_2 (56%); (k) $Ni(COD)_2$, Ph_3P, 90 °C (67%); (l) Red-Al, CuBr (74%); (m) BH_3·THF; PCC (48%).

of this methodology are under investigation and will be reported in due course.

Acknowledgment. Support for this work was provided by the National Science Foundation (CHE 83-19020). CRDC acknowledges the Brazilian National Research Council (CNPq) for a supporting fellowship (1981-1986). NMR spectra were obtained by using instrumentation supported by the National Science Foundation (CHE 84-14329).

Supplementary Material Available: Experimental details for the asymmetric reduction and the nickel-catalyzed cycloaddition of **3** and spectral and physical data for (***R***)-**6**, **3**, and **2** (4 pages). Ordering information is given on any current masthead page.

Stereoelectronic Effects at Carboxylate: A Syn Oriented Model for the Histidine-Aspartate Couple in Enzymes

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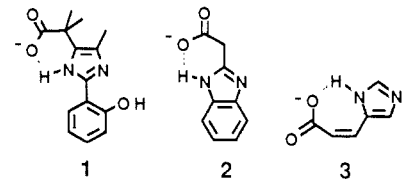
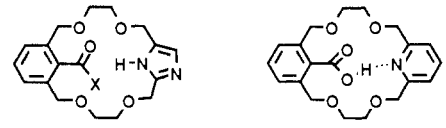
Features which recur in the active site of enzymes, unrelated by evolution, are particularly worthy of chemical modelling. It is essential, however, that these small organic molecules maintain the spatial relationships found in the enzymic system. Models of the serine proteases[1] (e.g., **1**[2a], **2**[2b], **3**[2c]) orient the anti lone pair of the carboxylate toward the imidazole, in contrast to the serine proteases,[3] malate and lactate dehydrogenase,[4] thermolysin,[5] and

Anti



Syn



DNAse I[6] which have all evolved to use His-Asp (Glu) couples with the N-3(H)-syn lone pair arrangement (Chart I).[7,8]

With respect to carboxylate orientation, Gandour has argued that there is a large stereoelectronic effect in operation whereby the carboxylate syn lone pair may be as much as 10^4 times more basic than the anti.[9,10] However, it is not known whether this will affect the pK_a of the His-Asp couple. In an elegant study, Craik has compared native trypsin with a mutant enzyme in which aspartate is replaced by neutral asparagine (D 102 N trypsin).[11] In this case, the carboxylate syn lone pair of Asp-102 increases the pK_a of His-57 by 1.5 units. In all anti imidazole-carboxylates the ΔpK_a, in aqueous medium,[12] is less than 1 pK_a unit. If the larger ΔpK_a seen in trypsin results from this syn orientation, then this could explain the preference seen for the N-3(H)-syn lone pair orientation in the enzymic His-Asp couple.

We wish to report the synthesis and pK_a determinations of **4**, the first syn oriented model of the enzymic His-Asp couple. Crucial to the design of our system was the X-ray structure of pyrido-crown ether **5**,[13] synthesized by Cram,[14] in which the benzoic acid moiety engages in a syn hydrogen bond with the pyridine nitrogen. A serviceable route to **4** involved the reaction of 1-benzylimidazole with formalin to produce 2,5-bis(hydroxymethyl)imidazole **6** (Scheme I).[15-17] Conversion to the bis(chloromethyl)imidazole hydrochloride and reaction with a large excess of ethylene glycol produced diol **7**, which was debenzylated

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