trisopropylsilyl group, the extent of stereocontrol was increased to 97:4:2.6. In all cases, effect of the ester group overrode the sense of enantioselection, following eq 2.

Certain aromatic substituents also affect the steric course. For example, when o-acetylbenzoic acid (1) was hydrogenated in the presence of an (R)-BINAP-Ru complex, the (R)-phthalide 3 was obtained in 92% ee and quantitatively. Surprisingly, o-bromoacetophenone afforded the (R)-alcohol 4 in 92% ee and in 97% yield, although unsubstituted acetophenone and the m- or p-bromo derivative failed to be hydrogenated in a satisfactory manner under the comparable conditions (<1% chemical yields and 74, 30, and 54% optical yield, respectively, with opposite enantioselectivity). The great rate enhancement with the o-bromo compound as well as the sense of enantioselection, following eq 2, indicates that even halogen atoms placed at appropriate positions in the substrates exert significant directing influence through interaction with Ru.

The aromatic halogen atom can be removed without racemization. The great rate enhancement with the o-bromo compound as well as the sense of enantioselection, following eq 2, indicates that even halogen atoms placed at appropriate positions in the substrates exert significant directing influence through interaction with Ru.

The aromatic halogen atom can be removed without racemization by CeCl₃-LiAlH₄ reduction. 12

When prochiral, symmetrical o- or p-diketones were subjected to the asymmetric catalysis, mixtures of the diols possessing meso and dl structures were obtained. The enantiomeric excesses of the dl isomers were uniformly high (99-100% ee). In a like manner, hydrogenation of unsymmetrical p-diketone 5 catalyzed by RuCl₂[(R)-binap] afforded (1S,3R)-diol 7 (92% yield, 94% ee) together with a small amount of (1S,3S)-diol 8 (6% yield, 54% ee). 13

In such two-step asymmetric hydrogenation of diketones, the overall stereochemical outcome is determined by both efficacy of catalyst/carbonyl chirality transfer (catalyst control) and structures of the initially created hydroxy ketones including chirality of the stereoactive center (substrate control). Hydrogenation of acetylacetone (6) catalyzed by RuCl₂[(R)-binap] produced first the (R)-hydroxy ketone 11 (98.5% ee at 10% conversion), as expected from eq 2, and then resulted in a 99:1 mixture of (R,R)-diol 8 in 100% ee and meso-diol 10. In contrast, hydrogenation of the isolated R Intermediate 11 (>99% ee) with the enantiomeric, (S)-BINAP-based catalyst led to the isomeric diols 8 and 10 in only 15:85 ratio. Thus the high enantiomeric purity of 8 obtained by the (R)-BINAP-Ru catalysis of 6 appears to be a result of double stereodifferentiation. 14 The analysis indicates that, in the second step, the catalyst control (33:1) is much more dominant over the substrate control favoring formation of dl-diols (6:1). 3-Methyl-2,4-pentanedione (12), an α-alkylated β-diketone, behaved like simple unsubstituted analogues. This asymmetric hydrogenation, viewed formally as triple stereodifferentiation, led to the dl-diol 13 (99% yield, 99% ee) and meso-diols (trace). In the reaction of a-diketones, substrate control in the second hydrogenation step, favoring meso-diol formation, becomes much more important, which results in high enantiomeric purities of the minor dl-diols products. Thus, (S)-BINAP-Ru aided hydrogenation of diacetyl (14) gave a 74:26 mixture of the meso-diol 15 and (S,S)-diol 16 in 100% ee.

The BINAP-Ru complexes have excellent kinetic chiral recognition ability and are capable of hydrogenating a series of functionalized ketones in a predictable manner and with satisfactory chemical and chiral efficiency. The high synthetic applicability is obvious.

Supplementary Material Available: Descriptions of the general procedures of the asymmetric hydrogenation using a 20-g scale reaction of acetylacetone as an example and determination of the enantiomeric excesses and absolute configurations of the products (13 pages). Ordering information is given on any current masthead page.

Synthesis of the Bicyclic Core of the Esperamicin/Calcichemicin Class of Antitumor Agents

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Received August 6, 1987

Over the past 10 years, considerable effort has been devoted to the elucidation of structure and mechanism of action of the potent antitumor protein complex neoeremophycin (nca) and its relative, aurmonycin. 3 The biological properties of nca reside completely within the highly unusual nonproteinaceous component, nos chromophore, 1 (Scheme 1). Edo has demonstrated that the DNA damaging properties of 1 can be traced to the bicyclic core comprised of an oxygenated enediine. 4 Recently, the structures of several members of a related class of DNA binding/damaging agents were simultaneously reported by chemists at Bristol-Myers 5 and Lederle. 6 The esperamicins (e.g., esperamicin A₁, 2) and calcicheamics share a common bicyclic core structure equipped with an enediyl bridge that is integral to the DNA damaging and extreme tumoricidal properties of these compounds. A novel

(2) Details of the structural determination are described in the Supplemental Material.
facilitate the design of damage via a hydrogen atom abstraction pathway.

ceeded to investigate a bicyclic core synthesis by the Diels-Alder addition of the resultant thiolate into the neighboring bridgehead core structures represent important targets for synthesis since the acquisition of such materials would pave the way for detailed consideration of plausible biogenetic origins of systems such as dichloroethylene by a route that forms three of the four bonds.

4), the esperamicin/calichemicin class of antitumor agents. Most revealing was the detailed 1H NMR spectrum that is recorded in the Supplementary Material.

The key core-forming cycloaddition was performed on the tert-butylidimethylsilyl derivative 13. Heating a 0.02 M solution of 13 in benzene at reflux temperature in the presence of Kishi's radical inhibitor afforded a 75% yield of the cycloadduct 15 as a 7:1 mixture of diastereomers.

A series of transformations related to those described for the synthesis of 15 was performed in order to produce the p-methoxyphenyl ether 16. The deprotection of 16 was achieved according to the conditions reported by Fukuyama.

Metalation with n-butyllithium and addition to the aldehyde derived from 9 resulted in the carbino11. Desilylation of 11 with tetrabutylammonium fluoride provided the corresponding terminal acetylene that was combined with methyl (E)-3-iodoacrylate to afford the labile Diels-Alder progenitor 12.

In summary, a concise and practical synthesis of the esperamin/calichemicin bicyclic core has been achieved. The modular nature of the reaction sequence is expected to provide access to a wide range of related systems. Investigations into the chemistry, biology, and pharmacology of nonnatural analogues are in progress.


Scheme I

Scheme II


Acknowledgment. These investigations were supported by the NSF (Presidential Young Investigator Award), the Alfred P. Sloan Foundation, and the Dreyfus Foundation (Teacher-Scholar Award, 1984–1989). Matching funds for the PYI were generously provided by Stuart Pharmaceuticals and Pfizer, Inc. We thank Dr. Terrence W. Doyle (Bristol-Myers Co.) for several stimulating discussions on this topic and Dr. Glen Spears for many helpful suggestions.

Supplementary Material Available: Spectral data and experimental procedures for 8–13 and 15–17 (10 pages). Ordering information is given on any current masthead page.

1,2,3,4,5,6-Tris(bicyclo[2.2.2]octene)tropylium I on: An All-Hydrocarbon Carboxation with Extraordinary Stability

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Received October 19, 1987

How much stability can be attained by a carboxation composed of only carbon and hydrogen? Here we report the synthesis of a new tropylium ion annelated with three bicyclo[2.2.2]octene units, which shows a pKt+ value of 13.0, the highest value ever recorded. Also described is a possible reaction pathway for the formation of its precursor, the highly symmetrical benzene dimer 5.

Continuous efforts have been made for the search of new carboxations possessing enhanced thermodynamic stability. So far, the cyclopropenyl cation substituted with guaiazulenyl1 or cyclopropyl groups2 is ranked as the most stable with a pKt+ value around 10.0. In the tropylium ion series, a-conjugative stabilization by poly(cyclopropyl) groups seems to be limited due to the saturation effects3 Nevertheless, it is more effective than p-conjugation,4 inductive electron donation,5 or intramolecular charge-transfer interaction.6 In this connection, it has been shown that the annelation with a bicyclo[2.2.2]octene unit is more effective in stabilizing the tropylium ion than that with a highly strained bicyclo[2.2.1]hexene unit.6 Thus, substantial stabilization is expected for the trisannelated cation 1.

For the synthesis of the precursor benzene 2, trimerization of bicyclo[2.2.2]octyne or its equivalent seemed feasible. Following the Gassman’s method for generation of norbornene,7 the dibromide 3b was lithiated with n-butyllithium at ~78 °C in THF and was treated with 10 mol % of nickelocene (or NiBr2(PPh3)2). After completion of the reaction by slowly warming to room temperature, they were isolated the cycloheptatriene,10 the dimeric dibromide 6 in yields of 33% and 18%, respectively. The rest of the products were a mixture of relatively low molecular weight bromides containing one to three bicyclooctene units, rather than high polymers. When 0.5 equiv of n-butyl lithium was used, the dimeric dibromide 5b was obtained in 34% yield in place of any appreciable amount of 2. These results suggest that 2 is formed not necessarily by trimerization of bicyclo[2.2.2]octyne but by way of consecutive coupling of the bicyclo[2.2.2]octene unit. This is supported also by the fact that 6 is quantitatively cyclized to 2 by the same procedure.

The CuBr-catalyzed ring expansion of 2 proceeded only by the use of a large excess (25 molar equiv) of diazomethane in refluxing 1,2-dichloroethane. The resulting cycloheptatriene,8 which was isolated in 15% yield (92% based on consumed 2) by chromatography over SiO2(93%–AgNO3(7%)), was treated with Ph3P=SbF6 to give the salt 1SbF6 in 91% yield.

The definitive upfield shifts observed for both the13C and1H NMR signals of the tropylium ring in 1 as compared with those in the bicyclo[2.2.2]octenotropylium ion 79 are indicative of decreased charge density on the cationic ring in 1 and its enhanced thermodynamic stability. The pKt+ value was then determined spectrophotometrically at 25 °C in a glycine (0.1 M)–NaOH (0.1 M) buffer prepared to pH 13.0. In accord with this, 1 undergoes no reaction with such nucleophiles as PhSH (pKt of the conjugate acid, 3.3), PhO- (9.9), CO2- (10.3), and Et3N (11.0). The enhanced stability of 1 is also demonstrated by its highly negative reduction potential (E1/2 = −1.120 V versus Ag/Ag+ in MeCN by cyclic voltammetry with a scan rate of 0.1

(8) All new compounds were characterized by their IR, UV,1H NMR, and13C NMR spectral data and elemental analyses and/or mass spectrometry. Selected spectral data for the important compounds are given below. For the full description of spectral data, see Supplementary Material. 1SbF6: mp 290–292 °C (dec); UV (MeCN) λmax 256 (log ε 4.71), 308 nm (4.01); 1H NMR (300 MHz, CDCl3) δ 8.85 (1H, s), 4.13 (2H, s), 4.07 (2H, s), 3.52 (2H, s), 2.05 (12H, d), 1.44 (12H, d); 13C NMR (25 MHz, CDCl3) δ 163.3 (s), 160.0 (s), 163.9 (s), 144.2 (d), 42.7 (d), 36.6 (d), 36.1 (d), 25.0 (d), 24.8 (s), 24.4 (d), 21.0 (s), 20.7 (s), 19.0 (s), 18.7 (s), 18.0 (s), 16.0 (s), 14.5 (s), 13.1 (s), 12.4 (s). 1SbF6: mp >300 °C; UV (MeCN) λmax 222 sh (log ε 3.62), 260 nm (24 T); 1H NMR (CDCl3) δ 4.39 (6H, s), 1.75 (12H, d), 1.35 (12H, d), 1.24 (12H, d), 1.23 (12H, d). 13C NMR (CDCl3) δ 134.2 (s), 28.7 (s), 26.5 (t). 5: mp 118–125 °C; 1H NMR (CDCl3) δ 2.76 (4H, s), 1.53 (16H, s); 13C NMR (CDCl3) δ 143.9 (s), 119.4 (s), 42.2 (s), 38.1 (d), 26.4 (t), 26.0 (d); 6: mp 156.0–158.0 °C; 1H NMR (CDCl3) δ 2.79 (2H, s), 2.60 (4H, d), 1.5–2.0 (12H, d); 13C NMR (CDCl3) δ 143.9 (s), 139.7 (s), 118.9 (s), 42.4 (d), 39.3 (d), 34.8 (d), 26.8 (s), 26.7 (t), 26.4 (s). 1SbF6: mp >300 °C; UV (MeCN) λmax 256 (log ε 4.72), 317 (3.93), 330 nm (3.01); 1H NMR (CDCl3) δ 3.89 (H, s), 2.82 (3H, s), 2.02 (12H, d), 1.42 (12H, d); 13C NMR (CDCl3) δ 164.9 (s), 162.6 (s), 162.4 (s), 162.3 (s), 36.6 (d), 36.0 (d), 35.8 (d), 24.8 (t), 24.7 (t), 24.6 (t), 24.55 (t). 9: mp 300 °C; UV (CDCl3) δ 8.98 (5H, s), 3.76 (2H, s), 2.11 (4H, d), 1.46 (4H, d); 13C NMR (CDCl3) δ 176.5 (s), 152.2 (d), 151.5 (d), 151.2 (d), 42.5 (d), 24.5 (s) (Nakazawa, T.; Niimoto, K.; Murata, I. Angew. Chem. 1980, 92, 545; Angew. Chem., Int. Ed. Eng. 1980, 19, 545 and ref 6).

(10) Averaged from triplicate values: 13.15, 13.29, and 12.88. This value was reproduced by using the phosphate–glycine–NaOH buffer and also for the perchlorate salt, 1-C104-. The neutralization was completely reversible, regenerating 1 after acidification. This value does not seem to be due to destabilization of the neutral precursor, since the steric constraint between the neighboring bicyclic units is even more severe in the planar cationic form than in the boat-shaped precursor cycloheptatriene.