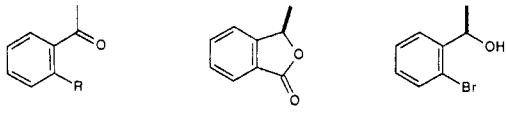
triisopropylsilyl group, the extent of stereocontrol was increased to 97.4:2.6. In all cases, effect of the ester group overrode the directivity of the alkoxyl or siloxyl functionality, and the sense of the chiral delivery consistently followed eq 2.

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



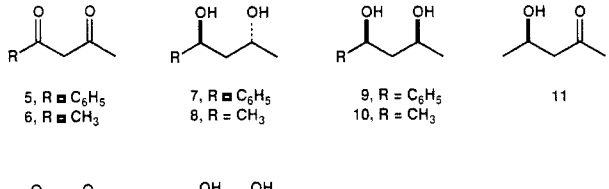
1, R = COOH
2, R = Br

3

4

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* enantioselection). 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 $CeCl_3$-$LiAlH_4$ reduction.[12]

When prochiral, symmetrical α- or β-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 β-diketone **5** catalyzed by $RuCl_2$[(*R*)-binap] afforded (1*S*,3*R*)-diol **7** (92% yield, 94% ee) together with a small amount of (1*S*,3*S*)-diol **9** (6% yield, 54% ee).[13]

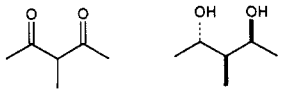


5, R = C_6H_5
6, R = CH_3

7, R = C_6H_5
8, R = CH_3

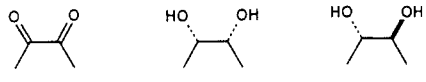
9, R = C_6H_5
10, R = CH_3

11



12

13



14

15

16

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 stereogenic center (substrate control). Hydrogenation of acetylacetone (**6**) catalyzed by $RuCl_2$[(*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 α-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*-diol 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.

Thus 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.

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(13) Details of the structural determination are described in the Supplementary Material.
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Synthesis of the Bicyclic Core of the Esperamicin/Calichemicin Class of Antitumor Agents

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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 neocarzinostatin (ncs)[1,2] and its relative, auromomycin.[3] The biological properties of ncs reside completely within the highly unusual nonproteinal component, ncs chromophore, **1** (Scheme I). Edo has demonstrated that the DNA damaging properties of **1** can be traced to the bicyclic core comprised of an oxygenated enediyne.[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.[6,7] The esperamicins (e.g., esperamicin A_1, **2**) and calichemicins share a common bicyclic core structure equipped with an enediyne bridge that is integral to the DNA damaging and extreme tumoricidal properties of these compounds. A novel

(1) Structure: (a) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Biochemistry: (b) Goldberg, I. H. In *Mechanisms of DNA Damage and Repair*; Simic, M. G., Grossman, L., Upton, A. D., Eds.; Plenum: New York, 1986; pp 231-244.
(2) The absolute stereochemistry of substituents on the methylene cyclopentene core is unknown. The *R*,*R*-stereochemistry depicted in **1** is the configuration predicted by a DNA binding model developed in our laboratory (manuscript in preparation). Modeling and synthesis research in this area was presented (by S.L.S.) at the 30th National Organic Chemistry Symposium of the American Chemical Society, Vancouver, Canada, June 21-26, 1987.
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(7) Related compounds include the following: (a) FR-900406 (Kiyoto, S.; Nishikawa, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H.; Kawai, Y.; Uchida, I.; Hashimoto, M. *J. Antibiot.* **1985**, *38*, 840). (b) PD 114759 (Bunge, R. H.; Hurley, T. R.; Smitka, T. A.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; French, J. C. *J. Antibiot.* **1984**, *37*, 1566) and PD 115208 (Wilton, J. H.; Rithner, C. D.; Hokanson, G. C.; French, J. C. *J. Antibiot.* **1986**, *39*, 1349).

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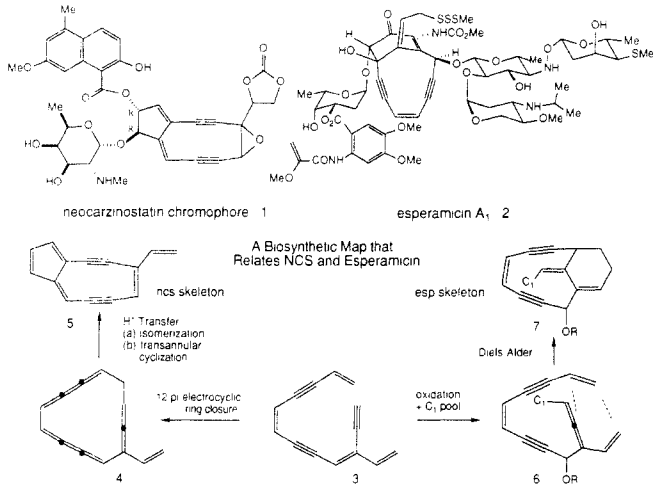
Scheme I



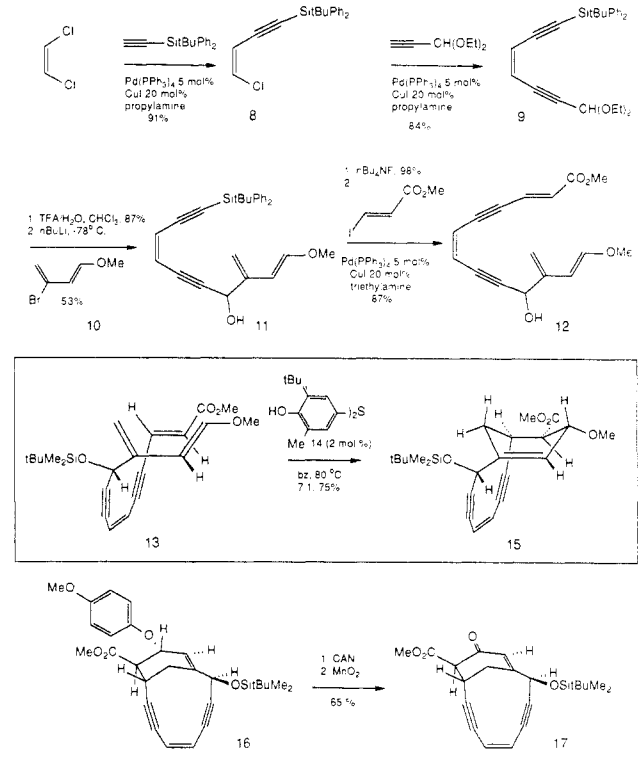
proposal for the mechanism of DNA strand cleavage was suggested to involve bioreductive cleavage of the allylic trisulfide and Michael addition of the resultant thiolate into the neighboring bridgehead olefin.[5,6] Such an action was proposed to facilitate coupling of the terminal sp carbons of the enediyne to form a phenylene diradical (Bergman reaction)[8] and ultimately result in DNA damage via a hydrogen atom abstraction pathway.

The chemistry of enediynes[8] *and the binding interactions*[2] *of systems such as* **1** *and* **2** *with DNA suggest a role for strained enediynes as potential nondiffusible DNA cleaving reagents*[9] *and facilitate the design of new chemotherapeutic agents.* The bicyclic core structures represent important targets for synthesis since the acquisition of such materials would pave the way for detailed investigations into their reaction chemistry, including their behavior toward double-stranded DNA fragments. Herein, we report on an efficient procedure for the synthesis of the bicyclic core of the esperamicin/calichemicin class of antitumor agents.

Our synthetic planning in this area was influenced by a consideration of plausible biogenetic origins of systems such as **1** and **2**. A possible common precursor to both classes is represented by **3**. NCS chromophore could be obtained from **3** by a series of transformations that include an electrocyclic ring closure (to **4**), proton transfer (to **5**), and oxygenation steps. The esperamicin/calichemicin class requires an additional carbon at the acetylene terminus of **3** (added in a manner to provide **6**). The vinylallene **6** (or oxidized equivalent) would be transformed into the esperamicin/calichemicin skeleton **7** by an intramolecular (Type 2) Diels–Alder reaction.[10] On inspection of models, it is evident that the enediynyl connector provides a favorable geometric constraint for the cycloaddition process. Accordingly, we proceeded to investigate a bicyclic core synthesis by the Diels–Alder pathway.

The synthesis of a cycloaddition precursor **12** is outlined in Scheme II. Compound **12** is available in six steps from (*Z*)-dichloroethylene by a route that forms three of the four bonds to the two acetylenes by application of the Castro–Stephans cross coupling reaction.[11] Monocoupling of dichloroethylene with *tert*-butyldiphenylsilylacetylene proceeded smoothly at 0 °C to provide the (*Z*)-vinyl chloride **8**. A second coupling (performed at room temperature) with diethoxy propargyl acetal delivered the (*Z*)-enediyne **9**. The diene component **10** is available from 1-methoxybuten-3-yne (Aldrich) by hydrobromination in ether.[12]

Scheme II



Metalation with *n*-butyllithium and addition to the aldehyde derived from **9** resulted in the carbinol **11**. 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**.

The key core-forming cycloaddition was performed on the *tert*-butyldimethylsilyl derivative **13**. Heating a 0.02 M solution of **13** in benzene at reflux temperature in the presence of Kishi's radical inhibitor **14**[13] afforded a 75% yield of the cycloadduct **15** as a 7:1 mixture of diastereomers. The stereochemistry at the propargylic center of the major isomer **15** was determined by NOE difference experiments and corresponds to that proposed for the esperamicins. The remaining stereocenters in **15** follow from the (geometry imposed) exo transition state in the Diels–Alder reaction.

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.[14] The resultant allylic alcohol was oxidized (MnO_2) to afford the bridgehead enone **17**. The spectroscopic data obtained from **17** are in full accord with the proposed structure. Most revealing was the detailed ^1H NMR spectrum that is recorded in the Supplementary Material. The bridgehead enone (present in **17**) is a striking feature of the esperamicin/calichemicin structures and has been proposed to play a central role in the priming mechanism for DNA damage. The synthesis of compounds related to **17** provides the opportunity to study (inter- and intramolecular) nucleophile-induced Bergman reactions of the cyclic enediyne according to the mechanistic proposals for the natural products. These studies are currently underway.

In summary, a concise and practical synthesis of the esperamicin/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.

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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]octeno)tropylium Ion: An All-Hydrocarbon Carbocation with Extraordinary Stability

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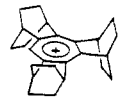
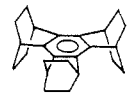
How much stability can be attained by a carbocation composed of only carbon and hydrogen? Here we report the synthesis of a new tropylium ion annelated with three bicyclo[2.2.2]octene units **1**, which shows a pK_{R^+} of 13.0, the highest value ever recorded. Also described is a possible reaction pathway for the formation of its precursor, the highly symmetrical benzene **2**.



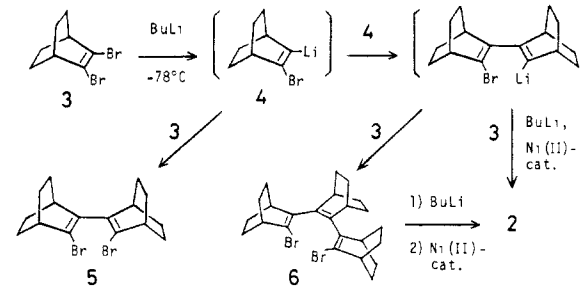
1



2

Continuous efforts have been made for the search of new carbocations possessing enhanced thermodynamic stability. So far, the cyclopropenylium ion substituted with guaiazulenyl[1] or cyclopropyl groups[2] is ranked as the most stable with a pK_{R^+} value around 10.0. In the tropylium ion series, σ-conjugative stabilization by poly(cyclopropyl) groups seems to be limited due to the saturation effect.[3] Nevertheless, it is more effective than π-conjugation,[4] inductive electron donation,[3] or intramolecular charge-transfer interaction.[5] 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[2.1.1]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 norbornyne,[7] the dibromide **3**[8] was lithiated with *n*-butyllithium at -78 °C in THF and was treated with 10 mol % of nickelocene (or $NiBr_2(PPh_3)_2$). After completion of the reaction by slowly warming to room temperature, there were isolated the expected benzene **2**[8] and the trimeric dibromide **6**[8] 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*-butyllithium was used, the dimeric dibromide **5**[8] 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 SiO_2(93%)-$AgNO_3$(7%), was treated with $Ph_3C^+SbF_6^-$ to give the salt **1**·SbF_6^-[8] in 91% yield.

The definite upfield shifts observed for both the ^{13}C and ^1H NMR signals of the tropylium ring in **1** as compared with those in the bicyclo[2.2.2]octenotropylium ion **7**[9] are indicative of decreased charge density on the cationic ring in **1** and its enhanced thermodynamic stability. The pK_{R^+} value was then determined spectrophotometrically at 25 °C in a glycine (0.1 M)-NaOH (0.1 M) buffer prepared in 50% aqueous MeCN (pH 10). By further alkalification with 20% NaOH, *the half-neutralization point, which corresponds to the pK_{R^+} value, was attained at pH 13.0.*[10] In accord with this, **1** undergoes no reaction with such nucleophiles as PhS^- (pK_a of the conjugate acid, 8.3), PhO^- (9.9), CO_3^{2-} (10.3), and Et_3N (11.0). The enhanced stability of **1** is also demonstrated by its highly negative reduction potential (E_{pc} = -1.120 V versus Ag/Ag^+ in MeCN by cyclic voltammetry with a scan rate of 0.1

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(8) All new compounds were characterized by their IR, UV, ^1H NMR, and ^{13}C NMR spectral data and elemental analyses and/or mass spectroscopy. Selected spectral data for the important compounds are given below. For the full description of spectral data, see Supplementary Material. **1**·SbF_6^-: mp 290-292 °C dec; UV (MeCN) λ_{max} 256 (log ϵ 4.71), 308 nm (4.01); ^1H NMR (300 MHz, CD_3CN) δ 8.55 (1 H, s), 4.13 (2 H, s), 4.07 (2 H, s), 3.56 (2 H, s), 2.05 (12 H, d), 1.44 (12 H, d); ^{13}C NMR (25 MHz, CD_3CN) δ 168.3 (s), 166.0 (s), 163.9 (s), 144.2 (d), 42.7 (d), 36.6 (d), 36.1 (d), 25.0 (t), 24.8 (t), 24.7 (t). **2**: mp 277-279 °C (sealed tube); UV (MeCN) λ_{max} 222 sh (log ϵ 3.62), 260 nm (2.47); ^1H NMR ($CDCl_3$) δ 3.29 (6 H, s), 1.75 (12 H, d), 1.35 (12 H, d); ^{13}C NMR ($CDCl_3$) δ 134.2 (s), 28.7 (d), 26.5 (t). **5**: mp 118-125 °C; ^1H NMR ($CDCl_3$) δ 2.76 (4 H, s), 1.53 (16 H, s); ^{13}C NMR ($CDCl_3$) δ 143.9 (s), 119.4 (s), 42.2 (d), 38.1 (d), 26.4 (t), 26.3 (t). **6**: mp 156.0-158.0 °C; ^1H NMR ($CDCl_3$) δ 2.79 (2 H, s), 2.60 (4 H, s), 1.50 (24 H, br s); ^{13}C NMR ($CDCl_3$) δ 143.9 (s), 139.7 (s), 118.9 (s), 42.4 (d), 39.3 (d), 34.8 (d), 26.8 (t), 26.7 (t), 26.4 (t). **8**·SbF_6^-: mp >300 °C; UV (MeCN) λ_{max} 262 (log ϵ 4.73), 317 (3.93), 330 nm (3.91); ^1H NMR (CD_3CN) δ 3.96 (6 H, s), 2.82 (3 H, s), 2.02 (12 H, d), 1.42 (12 H, d); ^{13}C NMR (CD_3CN) 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 (q), 24.55 (t).

(9) ^1H NMR (300 MHz, CD_3CN) δ 8.98 (5 H, s), 3.76 (2 H, s), 2.11 (4 H, d), 1.46 (4 H, d); ^{13}C NMR (CD_3CN) δ 176.5 (s), 152.2 (d), 151.5 (d), 151.2 (d), 42.5 (d), 24.5 (t) (Nakazawa, T.; Niimoto, Y.; Kubo, K.; Murata, I. *Angew. Chem.* **1980**, *92*, 566; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 545 and ref 6).

(10) Averaged from triplicate values: 13.15, 12.95, and 12.88. This value was reproduced by using the phosphate-glycine-NaOH buffer and also for the perchlorate salt, **1**·ClO_4^-. 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.

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