to intermacroion "attraction" caused by the counterion-macroion attraction as suggested by us.[2,10]

Finally we note the close similarity in the distributions in macroion systems and electrically charged monodisperse latex particle systems. For the latter, Hachisu et al.[14] demonstrated unequivocally the presence of fluctuating hexagonal or cubic ordered structure in solutions. Such an ordered structure we certainly be of the great significance for solution properties of not only synthetic polyelectrolytes but also ionic biopolymers in general. Further study is in progress.

Acknowledgment. Two of the authors (N.I. and T.O.) acknowledge valuable suggestions from Dr. F. Hamada. The small-angle X-ray scattering apparatus was constructed by a grant administered by the Ministry of Education to H.K.

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(12) The authors deeply thank Professor J. M. Schurr for his kind suggestion on the lattice spacing problem.
(13) The theoretical distance $2D_{th}$ was obtained by the following relation, $2D_{th} = 2(w/\pi N_A lc)^{1/2}$ and $2D_{th} = (2w/N_A lc \sin 60°)^{1/2}$ for the L-K and hexagonal lattice models, respectively, where c is the polyelectrolyte concentration in grams/milliliter, w and l are the weight and length of the monomeric unit, and N_A is the Avogadro number.
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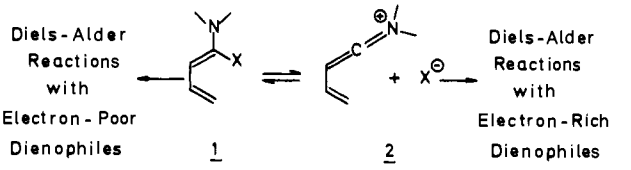
Diels–Alder Reactions of "Pull–Push" Activated Isoprenes

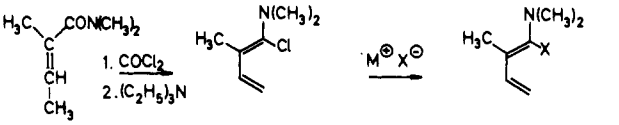
Sir:

1,1-Diheterosubstituted dienes have received only recently the degree of attention commensurate with their potentialities for the construction of highly functionalized rings by Diels–Alder cycloadditions. Such dienes are formally derived from vinylketenes which are too unstable and not accessible enough to be used successfully in Diels–Alder reactions.[1] The recently prepared vinylketenimines show a greater thermal stability and readily cycloadd to active dienophiles.[2] Vinylketene acetals[3–5] and thioacetals[6] have also been utilized as vinylketene equivalents in cycloaddition but were shown to react only with the most reactive dienophiles. However, the presence of an additional alkoxy or trimethylsilyloxy group at position 3 of the diene was found[4,7,8] to promote the reaction with less reactive dienophiles. 3-Hydroxy-2-pyrone has also been proposed[9] as a dienyl vinylketene equivalent, but its utility will probably be limited by the high temperatures (or pressures) required for the reactions with the less reactive dienophiles.

Scheme I. General Principle



Scheme II. Synthesis of 1,4 "Pull–Push" Isoprenes



4 (E + Z) 3 (E + Z) 5 to 10 (E + Z)

We reasoned that 1-amino-1-heterosubstituted dienes **1** should meet the requirements for a useful class of vinylketene equivalents (Scheme I).

The presence of an electron-donating amino group at C-1 should confer high reactivity and orientational selectivity on dienes **1** in their reactions with electron-poor dienophiles. In addition, our previous studies on α-haloenamines[10] suggested that **1** could readily equilibrate with a vinylketeniminium salt **2** provided that X is a suitable leaving group. Diene **2** would be expected to undergo Diels–Alder reactions with electron-rich dienophiles. Clearly, a proper choice of the basic strength of the amine substituent should enable control of both the electrophilic character at C-1 and the nucleophilic character at C-4 (1,4 pull–push character), whereas variation of X should permit selective control of each of these properties.[11]

This proposition has been reduced to practice. 1-Chloro-1-dimethylaminoisoprene (**3**) was readily prepared from *N,N*-dimethyltiglic or angelic amide (**4**) (Scheme II). Phosgene (10 mL, 0.14 mol) was added at −10 °C to a solution of **4** (12.7 g, 0.1 mol) in dry CH_2Cl_2 (100 mL). After 24 h at 20 °C, followed by removal of the solvent and excess of $COCl_2$ in vacuo (caution: no moisture!), the residue was redissolved in CH_2Cl_2 (final volume, ±50 mL). Triethylamine (21 mL) was added dropwise at −10 °C. Additional stirring (1 h) at 20 °C, addition of petroleum ether (100 mL, bp 70–100 °C), filtration under N_2, and distillation gave 11.6 g (80%) of diene **3** as a thermally stable but readily hydrolyzable liquid, bp 55 °C (12 mm), consisting of a mixture of *E* and *Z* isomers. NMR, δ_{CCl_4} (Me_4Si) major isomer, 7.00 (dd), 5.13 and 5.00 (dd + dd), 2.50 (s), 1.86 (s); minor isomer, 6.86 (dd), 5.23 and 5.13 (dd + dd), 2.50 (s), 1.91 (s) (J_{gem} = 1.5, J_{cis} = 12, J_{trans} = 20 Hz).

Compound **3**[12] behaved as methylvinylketeniminium chloride and displayed a high reactivity toward nucleophilic reagents. This provided a simple and practical route toward a series of activated isoprenes,[13,14] **5–10** (Table I).

The high electrophilic character of diene **3** is illustrated by its capacity of undergoing Diels–Alder reactions with unactivated nitriles (Scheme III). Thus, refluxing **3** (2 mmol) for 3 days in 5 mL of acetonitrile, followed by addition of triethylamine, yields 60% aminopyridine **11a**: NMR δ_{CCl_4} (Me_4Si) 2.2 (br s, 3 H), 2.3 (s, 3 H), 2.8 (s, 6 H), 6.5 (d, 1 H), 7.1 (d, 1 H). In the presence of KI, the cycloaddition occurred in 3 h. This clearly indicates that the reactive species adding across the C≡N bond is a vinylketeniminium chloride or iodide in equilibrium with **3** or, in the presence of KI, with **6** formed in situ. More interesting to us was the remarkable chemoselec-

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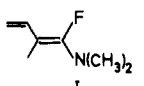
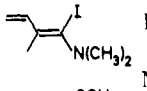
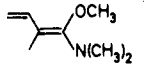
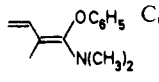
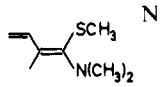
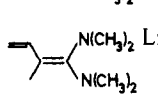
Table I. Synthesis of Activated Isoprenes from **3**

	product[a]	exptl conditions	yields, %	bp, °C (mm)
5		KF (2.5 equiv) in refluxing *o*-dichlorobenzene for 29 h	75[b,c]	57 (70)
6		KI (2.5 equiv) in refluxing benzene for 6 h	(. . .)[d]	
7		$NaOCH_3$ (2-3 equiv) in ether at 20 °C for 24 h *or* for 6 h in the presence of catalytic amount of KI	80-85[b]	67 (20)
8		C_6H_5OH (1 equiv) + $(C_2H_5)_3N$ (1 equiv) in ether at 20 °C for 1 h	70[b]	120 (18)
9		$NaSCH_3$ (2-3 equiv) in ether at 20 °C for 4 h in the presence of catalytic amount of KI	75[b]	84 (14)
10		$LiN(CH_3)_2$ (1 equiv) in ether-hexane at 25 °C for 1 h	83[e]	74 (13)

[a] Reference 13. [b] Pure distilled product. Both *E* and *Z* isomers are present. [c] Reference 15. [d] The mixture contains 80% **6** and 20% unreacted **3**. **6** is decomposed on distillation. [e] **10** is decomposed after a few hours at room temperature but can be distilled in a short-path apparatus. It can be kept at 20 °C in dilute benzene solution.

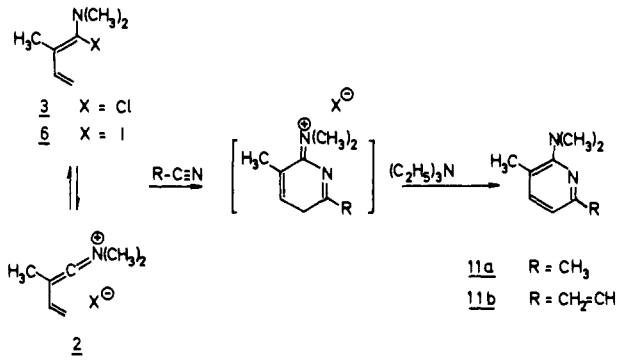
tivity of the reaction of **3** with acrylonitrile in the presence of KI which also gives a pyridine derivative **11b** in 62% yield: NMR δ_{CCl_4} (Me_4Si) 2.2 (br s, 3 H), 2.8 (s, 6 H), 5.2 (dd), 6.1 (dd), 6.56 (dd + d), 7.1 (d). This unusual preference of a diene for the C≡N bond of conjugated nitrile confirms the high propensity of compounds **3** and **6** to ionize and react as electrophilic dienes.

Remarkably, substitution of chlorine by fluorine in the diene leads to a complete reversal of the reactivity. Thus, the reaction of **5** with acrylonitrile in refluxing benzene occurred across the C=C double bond to yield, after hydrolysis, the "normal" Diels-Alder adduct **12a** in 69% yield: IR (film) $\nu_{C\equiv N}$ 2240, $\nu_{C=O}$ 1680, $\nu_{C=C}$ 1635 cm^{-1}; NMR δ_{CCl_4} (Me_4Si) 6.90 (m, 1 H), 3.70 (m, 1 H), 2.50 (m, 4 H), 1.80 (br s, 3 H) (melting point of the corresponding 2,4-dinitrophenylhydrazone, 172 °C) (Scheme IV). 5-Substituted 2-methylcyclohexenones **12a** and **12b** were obtained,[13] respectively, in 90 and 50% yields from the reaction of **10** with acrylonitrile and methyl acrylate.

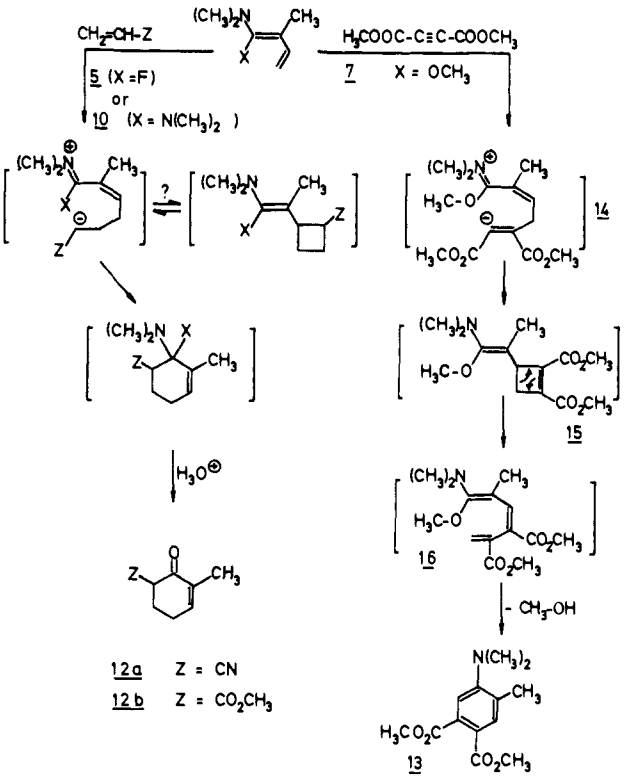
The exothermic reaction of diene **7** with dimethyl acetylenedicarboxylate in benzene at room temperature provided us with a surprising result. An aromatic product was obtained in 70% yield, which showed a substitution pattern incompatible with the normal Diels-Alder pathway. The NMR spectrum supported structure **13**: δ_{CDCl_3} (Me_4Si) 7.46 (s, 1 H), 7.06 (s, 1 H), 3.86 and 3.80 (2s, 6 H), 2.73 (s, 6 H), 2.31 (s, 3 H). This result may be understood[16] in terms of the formation of a stabilized dipolar structure **14** which, for steric or(and) conformational reasons, preferentially cyclizes to a cyclobutene intermediate **15**. Electrocyclic ring opening[17] followed by cyclization of **16** and aromatization readily account for the formation of **13**. A similar pathway could be invoked to explain the formation of **12a** and **12b** from **5** or **10** and electrophilic olefins. In such cases, the possible formation of a four-membered ring is expected to be reversible.[18] The reaction should therefore be driven toward the formation of the more stable six-membered rings.

We believe that a variety of synthetic applications should be expected from this new class of vinylketene equivalents. The possibility of adjusting the reactivity of the diene to specific needs is especially attractive and should further enhance the utility of the Diels-Alder reaction for the synthesis of highly functionalized six-membered rings. Further examples of 1,4 pull-push dienes as well as their utilization for the synthesis of cyclohexenones are in progress.

Scheme III. Diels-Alder Reactions of Electrophilic Isoprenes **3** and **6**



Scheme IV. Cycloaddition of Nucleophilic Isoprenes 5, 7, and 10



Acknowledgment. Financial assistance from the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (fellowship to M.G.) and the "Fonds National de la Recherche Scientifique" (fellowship to E.S.) is gratefully acknowledged.

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(14) Preliminary results indicate that the procedure outlined in Scheme II can be successfully applied to dienes bearing substituents at C-2. However it did not allow for the synthesis of $CH_2{=}CHCH{=}C(Cl)N(CH_3)_2$.
(15) Several perfluorinated derivatives of **5** have been obtained from the reaction of *N,N*-dimethylaminopropyne and perfluorinated olefins: Blazejewski, J. C.; Cantacuzene, D.; Wakselman, C. *Tetrahedron Lett.* **1974**, 2055-2058.
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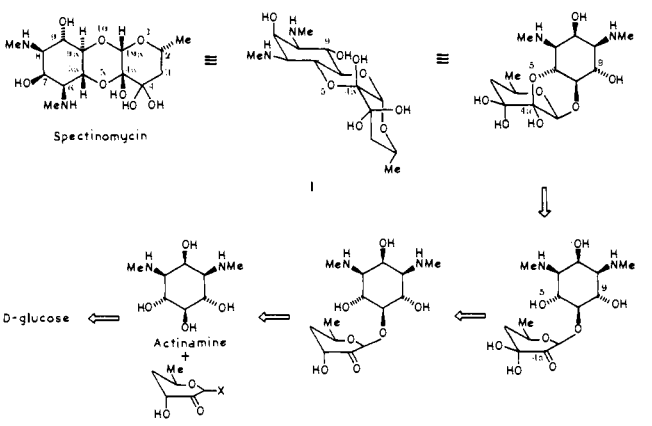
Synthesis of (+)-Spectinomycin

Sir:

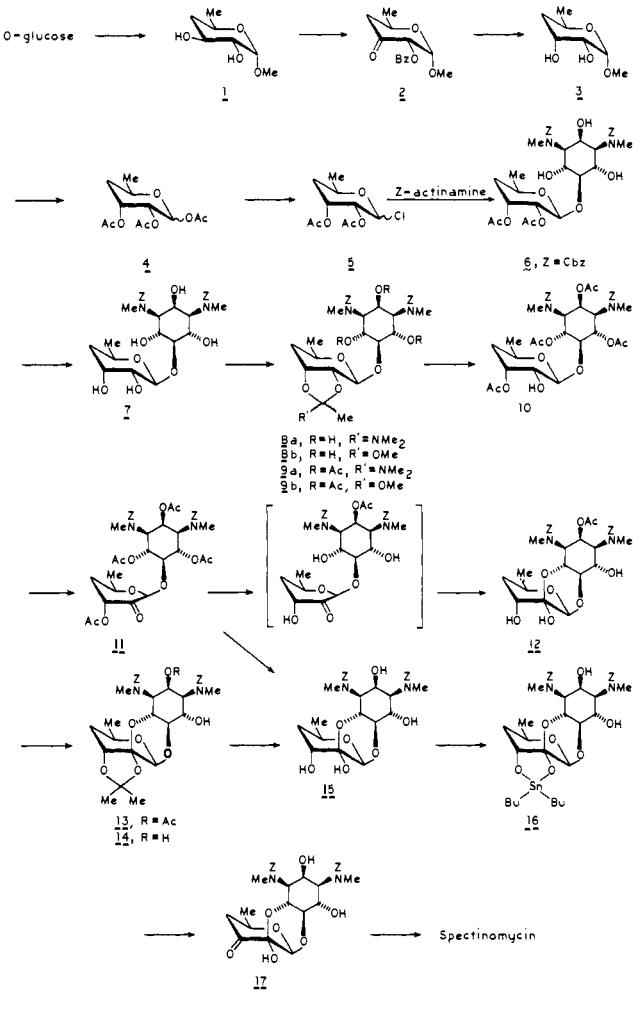
Spectinomycin (actinospectacin), isolated from a fermentation broth of *Streptomyces spectabilis* in 1961,[1] is perhaps structurally the most unique member of the medically important group of aminoglycoside antibiotics.[2] It is also endowed with an unusual biological property in that it exhibits a greater degree of therapeutic effect in infected animals than might be expected on the basis of its in vitro activities.[3] Widely used in the veterinary area, it also possesses potent activity against *Neisseria gonorrhoeae*, the gonorrhoea bacteria that has acquired resistance to penicillin and may be an alternate drug in such cases or for patients allergic to β-lactams.[4] The constitutional structure,[5] stereochemistry, and absolute configuration,[6] as well as the biosynthesis,[7] of spectinomycin have been the subject of elegant studies over the years. Its unique functional, stereochemical, and conformational features are depicted in different perspectives (Scheme I, expression I), where it can be seen that the fused tricyclic ring system contains nine chiral carbon atoms, each of which bears at least one heteroatom. A stereospecific synthesis of spectinomycin was recently disclosed by a group at Upjohn.[8] We now describe a new and stereospecific synthesis of spectinomycin, as well as of its 4(*R*)-dihydro, 4(*R*),4a(*R*)- and 4(*S*),4a(*R*)-tetrahydro derivatives, the first two being chemical precursors in the synthetic scheme leading to the antibiotic.

Our strategy called for the synthesis of one of the four[9] possible tetrahydrospectinomycins (4(*R*),4a(*R*) isomer), which

Scheme I



Scheme II



by virtue of a predisposed arrangement of hydroxyl groups was expected to provide the necessary regio- and stereocontrol in subsequent operations leading to a pivotal 4a-keto derivative of 4(*R*)-tetrahydrospectinomycin, and eventually to spectinomycin itself. With such a precursor in hand, we further expected the critical intramolecular ketalization[8] to be diastereoselective, owing primarily to a process of anomeric stereoselection.[10,11] These expectations were duly rewarded.

D-Glucose was transformed via a high-yielding sequence into the known[12] dideoxy derivative **1** (Scheme II). Sequential monobenzoylation ($(Bu_3Sn)_2O$, toluene, reflux 1 h; BzCl, room temperature, 30 min)[13] gave the known 2-benzoate, mp 103-105 °C (94%),[14] which was oxidized with pyridinium chlorochromate[15] (CH_2Cl_2, room temperature) to the 3-keto

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