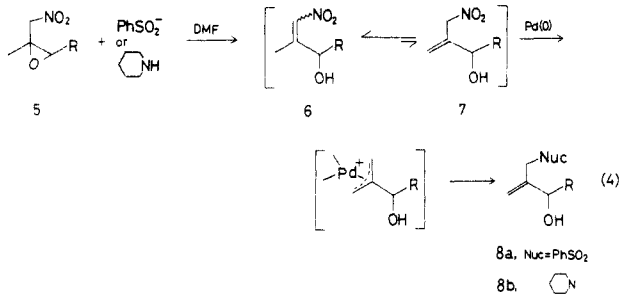
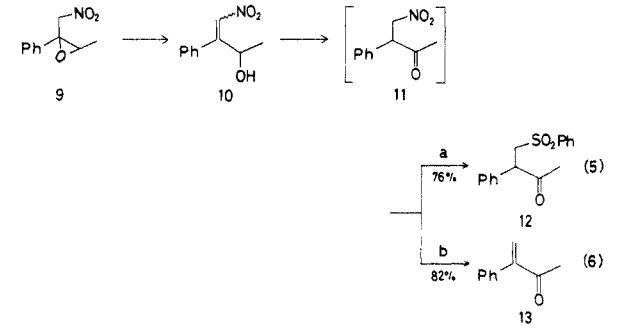


A typical experimental procedure for denito-sulfonylation follows: A mixture of 1-nitro-2-methyl-2,3-epoxybutane (5) (262 mg, 2.0 mmol), $PhSO_2Na{\cdot}2H_2O$ (600 mg, 3.0 mmol), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol), and dppe (24 mg, 0.06 mmol) in DMF (4 mL) was stirred at 70 °C for 2 h. The reaction mixture was partitioned between ether and water, and the aqueous phase was extracted with ether (3 × 30 mL). The ether extracts were washed with brine (3 × 30 mL) and water (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by column chromatography (1:1 hexane–ethyl acetate) gave 320 mg (71%) of 2-[(phenylsulfonyl)methyl]-3-hydroxy-1-butene (**8a**) as a pale yellow oil.

Thus, the presence of an alkyl group at the epoxy carbon β to the nitro group in the epoxy nitro compound to permit equilibration with an allylic nitro isomer is a mandatory requirement for these Pd(0)-catalyzed allylic substitutions to occur. In the case of 1-nitro-2-phenyl-2,3-epoxybutane (**9**) bearing a phenyl group at the β carbon atom, irrespective of the presence of Pd(0) catalyst, $PhSO_2^-$ reacted with **9** to give 3-phenyl-4-(phenylsulfonyl)-2-butanone (**12**) (eq 5). Moreover, treatment of **9** with excess Et_3N afforded the conjugated enone **13** (eq 6). These facts indicate that in the reaction of eq 5, $PhSO_2^-$ acts as a base to convert **9** to **13** via **10** and **11** and the concomitantly generated $PhSO_2H$ adds to **13** to produce **12**.



(a) 1.5 equiv of $PhSO_2Na{\cdot}2H_2O$, DMF, 70 °C, 3 h; (b) excess Et_3N, DMF, 70 °C, 24 h

The products 4 and 8 as well as **2** are believed to be useful synthetic intermediates owing to their possession of two allylic functional groups within a molecule. For example, hydroxy allylic sulfones **8a** are of interest in view of the recent studies on [3 + 2]-cycloaddition reactions.[8] Namely, the sulfones **8a** are the key intermediates for the Pd(0)-catalyzed cycloaddition with the activated olefins.[9]

Results described here attest to the ease of availability, the high reactivity, and the synthetic utility of β,γ-epoxy nitro compounds. Particularly, β-alkyl-β,γ-epoxy nitro compounds have been proven to serve as reactive substrates for Pd(0)-mediated denitro-sulfonylation and amination reactions. Further studies on this chemistry are in progress.

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Diels–Alder Cycloadditions Using Electrophilic Sulfonylpyridones

Summary: Examples are presented of 5–7-kbar [2 + 4]-cycloadditions of electrophilic 1,3-disulfonyl-2-pyridones with vinyl ethers leading regioselectively and stereoselectively to unsaturated, bridged, bicyclic lactams and, ultimately, to polyfunctionalized cyclohexanes.

Sir: We recently reported the first examples of Diels–Alder cycloadditions using an electrophilic 3-sulfinyl-2-pyrone[1] and an even more electrophilic 3-sulfonyl-2-pyrone,[2] with an application to a total synthesis of (−)-methyl triacetyl-4-epi-shikimate.[3] 2-Pyridones[4] have more aromatic character than 2-pyrones,[5] and consequently 2-pyridones generally do not enter effectively into [2 + 4]-cycloadditions.[6] It seemed appropriate, therefore, to determine

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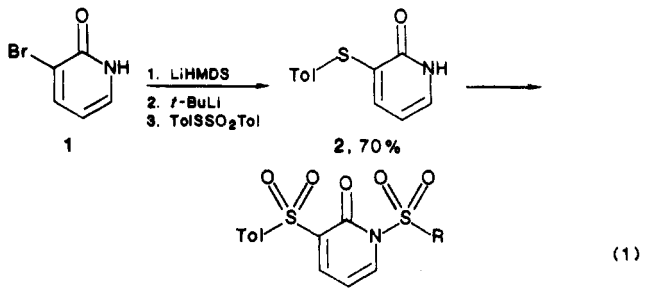
Table I. Sealed-Tube Cycloadditions via Equation 2

3	R	dienophile	solvent	temp (°C)	time (h)	% convn[a] to 4
a	*p*-tolyl	EVE[b]	CH_2Cl_2	100	40	56
b	*p*-BrC_6H_4	EVE	CH_2Cl_2	100	60	76
c	*p*-FC_6H_4	BVE[c]	toluene	90	34	40
d	*p*-$NO_2C_6H_4$	EVE	CH_2Cl_2	100	42	67
		BVE	toluene	90	40	78
e	C_6F_5	EVE	CH_2Cl_2	25	21	trace
				40	96	85
f	CF_3	EVE	CH_2Cl_2	25	14	46[d]
		EVE	CH_2Cl_2	57	14	26[d]

[a] Based on the relative ^1H NMR peak areas of the *p*-tolyl methyl group in product 4 vs. that in reactant 3. [b] Ethyl vinyl ether. [c] *n*-Butyl vinyl ether. [d] The major "product" appeared to be rearranged reactant (see text).

whether suitable sulfonyl groups[7] would make 2-pyridones sufficiently electron deficient to react with electron-rich dienophiles in inverse-electron-demand Diels–Alder cycloadditions.

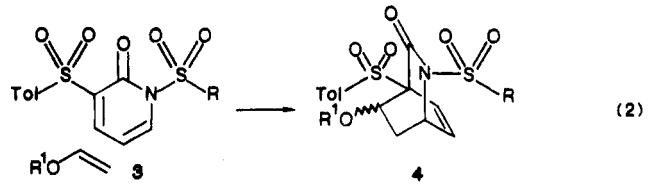
Diverse *N*-sulfonyl-3-(*p*-tolylsulfonyl)-2-pyridones **3a–f** were prepared via eq 1.[8] The effectiveness of the various



(1)

3, R = *p*-Tol, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, C_6F_5, CF_3
a b c d e f

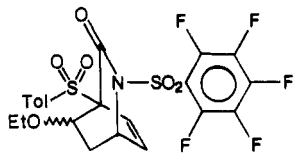
N-sulfonyl groups as electron-withdrawing substituents in promoting Diels–Alder cycloaddition with an electron-rich dienophile such as ethyl or *n*-butyl vinyl ether was assayed qualitatively via eq 2; the results are tabulated in Table

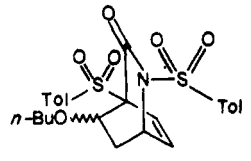


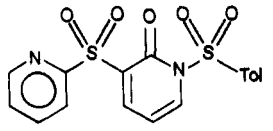
(2)

I. Several generalizations emerge from these experiments: (1) the fundamental rationale for this project is proved correct by the successful cycloadditions in Table I; (2) all of the para-substituted (phenylsulfonyl)pyridones (i.e., **3a–d**) have roughly comparable reactivity; (3) the polyfluorinated sulfonylpyridones **3e** and **3f** are more reactive than the para-substituted (phenylsulfonyl)pyridones; the (trifluoromethyl)sulfonyl derivative **3f** shows substantial reactivity even at 25 °C, but the reactant undergoes an N → O sulfonyl migration that is competitive with the Diels–Alder reaction.[9]

In the cycloadditions where elevated temperatures were used, polymerization of the reactant vinyl ether was observed. This polymerization was found to retard the progress of the reaction. The use of additives such as triethanolamine, diphenylamine, hydroquinone, or barium carbonate (which was the most effective in limiting polymerization) afforded no improvement in the yield of the cycloadduct. A scale-up of the procedure used in the initial assay with *N*-[(pentafluorophenyl)sulfonyl]pyridone derivative **3e** led to a 58% isolated yield of the major adduct diastereomer **4e**. Unfortunately this yield was not reproducible, and this lack of reproducibility is most readily attributable to initiation of the vinyl ether polymerization at differing times during the cycloaddition reaction.







Lewis acid catalysis often facilitates Diels–Alder cycloadditions.[10] Zinc dibromide, zinc acetylacetonate, cerium(III) chloride, titanium tetraisopropoxide, and lithium triflate were tried without any improvement in cycloadduct yield. 3-(Pyridylsulfonyl)-2-pyridone **5** was prepared in the hope that Lewis acid coordination[11] and therefore possibly Diels–Alder cycloaddition would be especially favorable; cycloaddition with *n*-butyl vinyl ether was not improved even in the presence of trimethylaluminum, zinc acetylacetonate, or boron trifluoride etherate.

Medium and high pressures usually facilitate reactions with negative volumes of activation such as Diels–Alder cycloadditions.[12] *N*-[(Pentafluorophenyl)sulfonyl]-pyridone **3e** reacted with ethyl vinyl ether (which was not polymerized) at 25 °C for 6 h at 7 kbar of pressure to produce cycloadduct **4e**, which was isolated in 89% yield as a 5.4:1 mixture of endo and exo isomers. *N*-Tosylpyridone **3a** reacted similarly with butyl vinyl ether at 5 kbar and 50 °C for 56 h to form cycloadduct **4a** on a several hundred milligram scale in 78% yield as a 6.8:1 mixture of endo:exo isomers (with respect to the ethylenic bridge).[6m] *These are the first examples of effective [2 + 4]-cycloadditions of 2-pyridones with electron-rich dienophiles.*

(7) *N*-Acetyl-2-pyridone rearranges at 25 °C into 2-acetoxypyridine: McKillop, A.; Zelesko, M.-T.; Taylor, E. C. *Tetrahedron Lett.* **1968**, 4945; cf. Singth, P. A.; Janssen, M. J. *Ibid.* **1971**, 4223.

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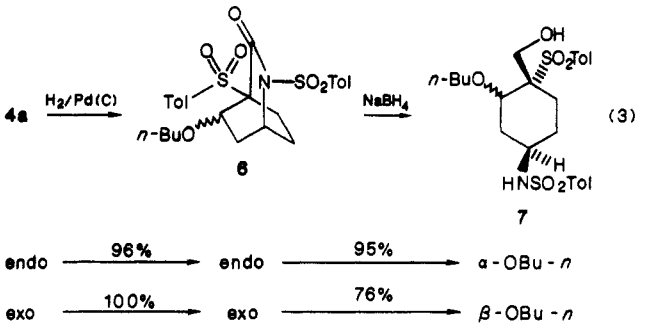
We expect that using alkyl vinyl ethers in which the alkyl group is bulkier than ethyl or *n*-butyl will lead to even higher endo:exo ratios in the cycloadducts. Cycloadducts **4a** and **4e** are richly functionalized, bridged, bicyclic lactams that should undergo a variety of chemoselective and stereoselective operations. For example, hydroxylation of the olefinic bond in these unsaturated lactams and opening of the lactam bridge would produce trioxygenated aminocyclohexanes structurally related to some antibiotic aminocyclitols.[13] As preliminary evidence that such unsaturated bicyclic lactams can be manipulated efficiently, cycloadducts *endo*-**4a** and *exo*-**4a** were separately catalytically hydrogenated to produce bicyclic lactams *endo*-**6** and *exo*-**6**, which were reductively cleaved by sodium borohydride[14] to form polyfunctionalized cyclohexanes 7α and 7β (eq 3).



Analysis of the 400-MHz ^{1}H NMR spectra of cyclohexyl butyl ethers 7α and 7β supported the stereochemical assignment of the major isomer as 7α and therefore the major cycloadduct **4a** as *endo*-**4a**, as expected in analogy to our results in the corresponding 3-sulfonyl-2-pyrone cycloadditions.[2,3] Specifically, isomer 7α showed a ^{1}H NMR peak for C*H*OBu at δ 3.73 with a width at one-half height ($W_{1/2}$) of 7.3 Hz characteristic of an equatorial hydrogen atom,[15,16] whereas isomer 7β (in which the more stable chair conformation has three equatorial substituents including the *n*-butoxy group) showed a peak at δ 4.02 (dd, J = 7.87, 3.77 Hz) with $W_{1/2}$ = 12.2 Hz.

We intend to apply these sulfonylpyridones to asymmetric cycloadditions in order to prepare aminocyclohexanols of high enantiomeric purity.

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Supplementary Material Available: Experimental details for preparation of **3**–**7** and spectroscopic and analytical data (21 pages). Ordering information is given on any current masthead page.

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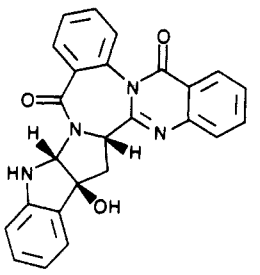
Total Synthesis of Nonpeptidal Cholecystokinin Antagonists from *Aspergillus alliaceus*†

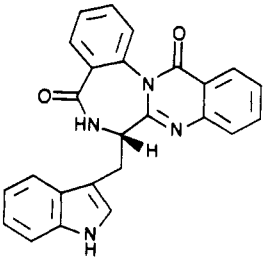
Summary: Two quinazolino-1,4-benzodiazepines isolated from *Aspergillus alliaceus*, which are antagonists of the peptide hormone cholecystokinin, have been synthesized from L-tryptophan and anthranilic acid.

Sir: Cholecystokinin (CCK), a 33-amino acid neuropeptide,[1] is a hormonal regulator of gall bladder contractility and of pancreatic enzyme secretion.[2] The discovery of the wide distribution of this gastrointestinal hormone in the brain[3] has aided in formulating the hypothesis that it may also function as a neurotransmitter or neuromodulator in the central nervous system.[4] Thus, CCK has been implicated in a variety of physiological functions such as satiety sensation,[5] sedation,[6] and analgesia.[7]

In this paper, we report the synthesis of two agents (**1** and **2**), isolated from a microbial source,[8] which are receptor antagonists of CCK.[9] These compounds are conceivably related biogenetically to the recently described CCK antagonist, asperlicin,[10] and constitute two additional examples of an emerging group of nonpeptidal compounds which are now recognized to be ligands for peptide hormone receptors.[11,12] The chemical structures of the title compounds **1** and **2** were deduced spectroscopically.



1



2

Our synthetic strategy for preparing **1** was based on the premise that it could be derived via intramolecular oxidative cyclization of **2**. Further disconnections of strategic bonds in **2** revealed that it, in turn, could be simplified to anthranilic acid and L-tryptophan. While alternative analyses can be envisioned, this plan suggested an approach which could be readily tested and, importantly, would afford intermediates which could be diverted to other synthetic objectives.

Reaction of isatoic anhydride **3** with L-tryptophan in water, in the presence of triethylamine, afforded the corresponding *N*-anthranoyl-L-tryptophan derivative (Scheme I). All volatile materials were then removed under reduced pressure and, without isolation of the intermediate, the resulting residue was heated in glacial acetic acid to give the benzodiazepinedione **4** (90% overall).[13,14] Further elaboration of **4** to give **2** required a regioselective annulation with anthranilic acid. This was accomplished in three steps by first reacting **4** with the Lawesson reagent[15] in tetrahydrofuran to give **5**[14] (33%) and an equivalent amount of the readily separable regioisomeric thionamide. The thionamide **5** was then transformed with iodomethane under phase-transfer conditions to the corresponding methyl imino thioether **6** (74%). In the final step, a mixture of crystalline **6** and methyl anthranilate was heated (neat) for 1 h to give **2** in 83% yield.[14,16] These

† Dedicated to Professor George Büchi on the occasion of his 65th birthday (J.P.S., R.M.F.).

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