A Thioxanone-Based Chiral Template: Asymmetric Induction in the [2,3]-Sigmatropic Rearrangement of Sulfur Ylids. Enantioselective Preparation of Cβ-Chiral Pent-4-enoic Acids[1a]

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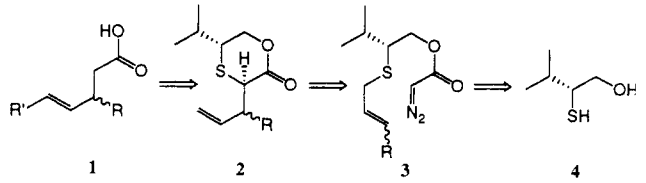
Summary: A thioxanone-based [2,3]-sigmatropic rearrangement strategy which delivers Cβ-chiral pent-4-enoic acids with excellent Cβ-induction is reported.

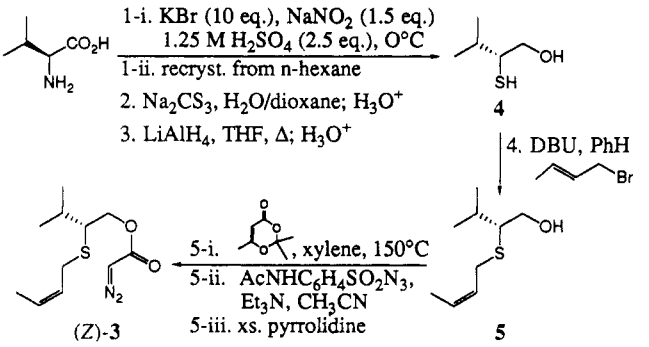
Previous publications[2] from these laboratories established the aza-Claisen rearrangement as a versatile enantioselective route to Cα- and Cβ-chiral pent-4-enoic acids (**1**, R′ = H) where Cα-induction was uniformly high (≈97% de) while Cβ-induction was variable (70–97% de) reflecting substrate-dependent chair/boat selectivity. Likewise, chirality transfer in Ireland's ester enolate Claisen rearrangement[3] of enantiomerically pure allylic alkanoates delivers Cα- and Cβ-chiral pent-4-enoic acid derivatives[4] with the caveat that the allylic system be derived from a chiral secondary alcohol with the consequence that **1** must be Cδ substituted (i.e., R′ ≠ H). In 1984, Ireland and Varney[5] reported a silyl-assisted asymmetric ester enolate Claisen route to **1** (R′ = H) which redressed this limitation with an R′ = Si(ᵗBu)Me$_2$ → R′ = H transformation; a clever strategy which is, however, bottlenecked by requiring MTPA ester resolution of the HOCH(Si(ᵗBu)Me$_2$)CH=CHCH$_3$ racemate. Herein we report a thioxanone-based [2,3]-sigmatropic[6] rearrangement strategy which delivers Cβ-chiral pent-4-enoic acid **1** (R′ = H) with excellent Cβ-induction and without the requirements of an allylic alcohol resolution.



1 **2** **3** **4**

In planning this strategy, three key questions emerged. Would enantiomerically pure hydroxy thiol **4** be readily available from L-valine and would its elaboration to α-diazo ester **3** be straightforward? Could conditions be defined which would convert **3** to thioxanone **2** via the intermediacy of a sulfur ylid? Finally, could **2** be disassembled in a manner which would deliver the desired pent-4-enoic acid **1** (R′ = H) and at the same time liberate hydroxy thiol **4** for recycling? If so, this method would constitute a chiral auxiliary-mediated, enantioselective route to **1**.

Scheme I



Starting with L-valine, diazonium formation[7] in the presence of excess potassium bromide gave an ≈12:1 mixture of 2-bromoisovaleric acid and 2-hydroxyisovalaric acid, respectively. Recrystallization from *n*-hexane delivered the pure bromide with retention of configuration in 55% yield. Nucleophilic displacement with sodium trithiocarbonate[8a] followed by acid-catalyzed hydrolysis of the trithiocarbonate moiety and LAH reduction of the resulting carboxylic acid furnished hydroxy thiol **4** in 78% overall yield (Scheme I). Simple *S*-alkylation[8b] of this unpleasant smelling oil with (*Z*)-crotyl bromide gave sulfide **5** in 93% yield. Elaboration to α-diazo ester (*Z*)-**3** was accomplished as a two-pot operation in 75% overall yield as follows. Acetoacetylating the primary hydroxyl of **5** with the commercially available acetylketene precursor 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in refluxing xylene[9] delivered the acetoacetate of **5**. Diazotization of this active methylene compound with *p*-(*N*-acetylamido)benzenesulfonyl azide[10] and triethylamine in acetonitrile gave the corresponding α-diazo-β-keto ester which was, without isolation, deacylated with excess pyrrolidine[11] to (*Z*)-**3**. In fact, **5** → **3** can be accomplished in a one-pot procedure with no isolation of intermediates by sequential addition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, *p*-(N-acetylamido)benzenesulfonyl azide/triethylamine/acetonitrile, and pyrrolidine to a xylene solution of sulfide **5** in 83% yield.

Having resolved the "L-valine → α-diazo ester **3**" question, attention was turned to the **3** → **2** transformation; an interconversion which encompasses heterocycle formation and [2,3]-sigmatropic rearrangement. Clearly the success of this multifarious transformation would be bracketed by two interrelated control elements, diastereoselectivity in the heterocyclization (i.e., C–S bond formation) and diastereoselectivity in the [2,3]-sigmatropic

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(4) See for example: (a) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. (b) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479.

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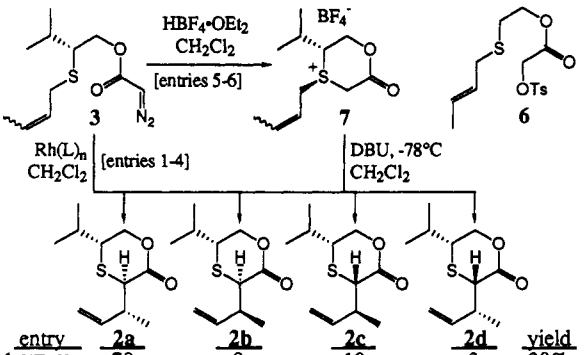
rearrangement (i.e., C–C bond formation), as well as its overall efficiency. Taking cue from the studies of Vedejs,[12] Doyle,[13] Davies,[14] and Moody,[15] our first efforts enlisted rhodium-promoted metallocarbene formation as preemptor to a heterocyclization with concomitant sulfur ylid formation/[2,3]-sigmatropic rearrangement cascade. Indeed, rhodium(II) acetate catalyzed decomposition of (*Z*)-**3** produced the four possible thioxonones in only 30% combined yield, and the major isomer (**2a**) was produced in a disappointing 78% diastereoselectivity[16] (ds; see entry 1 in Scheme II). Slightly improved diastereoselectivity, but not yield, was obtained with hexarhodium hexadecacarbonyl as catalyst (entry 2 in Scheme II) and parallel results were obtained starting with (*E*)-**3** except here the major isomer was thioxonone **2b**[17] (entries 3 and 4 in Scheme II). Thus, the allure of these one-pot rhodium-catalyzed **3** → **2** transformations was diminished by the moderate ≈9:1 (i.e., (**2a** + **2b**):(**2c** + **2d**)) diastereoselectivity of the heterocyclization step, the apparent variable face selectivity of the sigmatropic rearrangement (7–11:1 = **2a**:**2b**), and disappointingly low yields.

In light of these apparent metal–carbene deficiencies, attention was directed to a stepwise strategy which called for (i) an acid-catalyzed heterocyclization step, (ii) ylid formation, and (iii) [2,3]-sigmatropic rearrangement. In the first step, protonation of the α-diazoacetate moiety followed by nucleophilic displacement of N_2 by sulfur was envisioned to give a thioxonium intermediate.[18] However and to our surprise, *p*-toluenesulfonic acid resulted in nucleophilic displacement of N_2 by the conjugate base (*p*-$TolSO_3^-$) producing α-tosylacetate **6** instead of the the desired thioxonium salt. In contrast and to our delight, tetrafluoroboric acid–diethyl ether complex avoids this conjugate base problem and delivers the desired thioxonium salt **7** as what appears to be *one diastereomer*.[19] Simply treating this cold HBF_4·Et_2O reaction mixture with DBU furnished thioxanones **2a–d** in good overall yield and with excellent diastereoselectivity, **2a** coming from (*Z*)-**3** in 94% ds and **2b** coming from (*E*)-**3** in 93% ds (entries 5 and 6, respectively, in Scheme II).[20] These are "kinetic ratios" since treating a 94:5:1:0 = **2a**:**2b**:**2c**:**2d** mixture with a catalytic amount of DBU in CH_2Cl_2 resulted in equilibration to a 61:3:2:34 = **2a**:**2b**:**2c**:**2d** mixture.

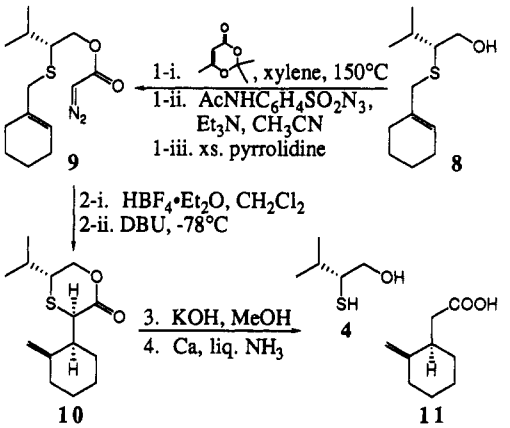
All that remained was to disassemble **2** in a manner which delivered both the targeted Cβ-chiral pent-4-enoic

Scheme II



entry	2a	2b	2c	2d	yield
1 [(*Z*)-**3**]	78	9	10	3	30%
2 [(*Z*)-**3**]	84	8	7	1	35%
3 [(*E*)-**3**]	10	70	5	15	30%
4 [(*E*)-**3**]	10	83	2	5	28%
5 [(*Z*)-**3**]	94	4	2	trace	66%
6 [(*E*)-**3**]	4	93	1	2	64%

Scheme III



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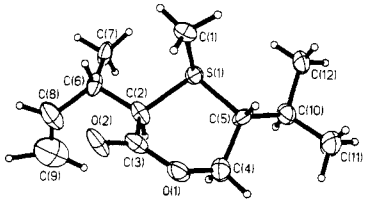
(16) (a) Thioxanone ratios were determined by capillary GLC analysis [flame ionization detection using a 15 m × 0.329 mm DB1701 column, helium carrier gas, 240°C detector temperature, 220°C injector temperature, and oven temperature programmed at 110 $°C_{initial}$ + 2 °C/min: **2c** at 13.3 min, **2d** at 13.5 min, **2a** at 14.5 min, and **2b** at 14.6 min]. (b) Stereochemical assignments for **2a–d** were made as follows. **2b**: X-ray crystal analysis of the corresponding *S*-methyl thioxonium salt (**2b-X**; see note 17). **2c**: base-catalyzed Cα-isomerization of **2b** produces **2c**. **2a**: (*E*)-**3** gives **2b** as the major product (Scheme III, entry 6), so it follows that (*Z*)-**3** gives **2a**, the Cβ-epimer of **2b**, as the major product. **2d**: base-catalyzed Cα-isomerization of **2a** produces **2d**.

(17) The relative stereochemistry of **2b** was determined by X-ray crystal analysis of the corresponding *S*-methyl thioxonium salt (**2b-X**), in turn prepared by treating these thioxonones with methyl trifluoromethanesulfonate in CH_2Cl_2. X-ray crystallographic data are available as supplemental material



2b-X (triflate counterion)

space group	$P2_12_12_1$
crystal system	orthorhombic
Z	4
a	7.562 (2) Å
b	12.765 (4) Å
c	17.542 (6) Å

(18) Retitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: New York, 1986, Chapter 3.

(19) Based on the product selectivity of this **3** → **2** sequence, thioxonium intermediate **7** must be formed with the isopropyl and crotyl trans to one another.

(20) Procedure for (*E*)-**3** → **2**: Commercially available 85% HBF_4·OEt_2 (170 mg) was added dropwise to a stirred solution of (*E*)-α-diazoacetate **3** (230 mg, 0.95 mmol) in dry CH_2Cl_2 (20 mL) at room temperature under nitrogen atmosphere. Evolution of gas (N_2) was observed during the addition, and the reaction solution turned from pale yellow to colorless. TLC analysis revealed complete disappearance of the starting α-diazoacetate ester and appearance of a new spot at the base line. Then, after cooling this solution to −78 °C, DBU (180 μL, 183 mg, 1.20 mmol) was added, and stirring continued at −78 °C for ≈10 min at which time TLC revealed a new spot with a R_f of 0.31 (7:1 hexane–EtOAc). Acetic acid (10% in dichloromethane, 3 mL) was added at −78 °C, and the resulting mixture was transferred to a separatory funnel, washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to dryness. The residual oil was purified by flash chromatography using a 7:1 hexane–EtOAc eluant.

acid 1 and the chiral auxiliary 4. While over reduction with Raney nickel and only marginal selectivity between the two thioxanone C-S bonds with tributyltin hydride were disappointing, an ester saponification/calcium (2 equiv) in liquid ammonia reduction[21] sequence worked nicely regenerating the unchanged chiral auxiliary in 84% yield and liberating the pentenoic acid in 69% yield and 88% ee. Not suprisingly, the saponification step causes some epimerization of the Cα-stereocenter, but this is of no consequence since this stereocenter is removed in the C-S reduction step. The salient features of this four-step, three-pot conversion of α-diazo ester 3 to Cβ-chiral pent-4-enoic acid 1 are nicely illustrated in Scheme III for 9 → 11 (39% overall yield).

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Supplementary Material Available: Spectral data for **2b**, (*Z*)-**3**, **4**, and **5** as well as X-ray crystallograhphic data for *S*-methyl thioxonium salt **2b-X** (13 pages). Ordering information is given on any current masthead page.

Articles

SINDO1 Study of the Photoisomerization of 2-Cyanopyrrole to 3-Cyanopyrrole

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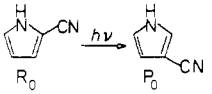
The mechanism of the photochemical isomerization of 2-cyanopyrrole to 3-cyanopyrrole was investigated with the semiempirical MO method SINDO1. Potential energy hypersurfaces of excited states and transition structures of the ground state were calculated with limited configuration interaction (CI) for a qualitative explanation of the reaction pathway. The first reaction step is an internal cyclization which occurs via a minimum on the first excited singlet surface. From there a radiationless transition leads to the ground-state surface. On the ground-state surface either a back reaction to the reactant or a [1,3] sigmatropic shift of the NH group takes place. The latter forms 2-cyano-5-azabicyclo[2.1.0]pentene, which reacts by ring opening to 3-cyanopyrrole. This rearrangement mechanism is unfavorable for furan because the barrier for the 1,3-oxygen migration is much higher than for rearomatization.

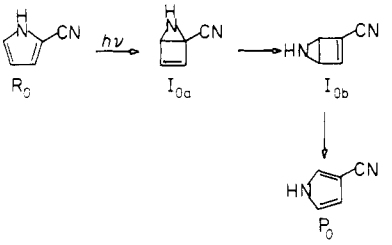
Introduction

In the photoisomerization reaction of many heterocyclic five-membered aromatic rings a permutation of ring atoms takes place. Frequently two neighboring atoms are exchanged. Different product yields and byproducts are obtained dependent on the heteroatom in the ring. As explanation for this fact, different reaction mechanisms were proposed for different heterocycles.[1]

2-Cyanopyrrole reacts under radiation with UV light to 3-cyanopyrrole with a yield of 55%.[2] The reaction is temperature dependent; no isomerization takes place at −68 °C.[2-4]



The following internal cyclization–isomerization mechanism was proposed: As a first step a bond between atoms $C_{(2)}$ and $C_{(5)}$ is formed. The second reaction step



is a [1,3] sigmatropic shift of the NH group followed by the ring opening to 3-cyanopyrrole.

Nishimoto et al. have reported in ab initio calculations[5,6] about the internal cyclization mechanisms for oxazole and thiophene. For oxazole a participation of a triplet state in the reaction was found; for thiophene is was found that the [1,3] sigmatropic shift occurs on an excited surface. For pyrrole the experimentalists[2-4] have no indication for the participation of a triplet state and the [1,3] migration of the NH group is considered as a thermal reaction, i.e. on the ground-state surface. Skancke[7a,b] has investigated

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