## STEREOSPECIFIC TOTAL SYNTHESES OF $7\alpha$ - AND $7\beta$ -EREMOPHILANE-6-ONE AND $7\alpha$ - AND $7\beta$ -EREMOPHILANE

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<u>Summary</u>: The title compounds have been prepared in a highly efficient fashion by a synthetic route involving an intramolecular Diels-Alder reaction of an acetylenic thiazole followed by reductive modification of the resulting fused-ring thiophene.

Raney-nickel desulfurization is a well established technique for the conversion of thiophenes to aliphatic ketones, alcohols, or hydrocarbons, in which the regiochemical features of the derived carbon skeleton are unequivocally related to the substitution pattern of the heterocyclic template (*cf.* A ---> B, below, X = O, H<sub>2</sub>).<sup>1</sup>



The potential utility of this methodology is aptly illustrated for the case where  $R_1 = H$  and  $R_2 = Me$ , wherein the 3methylthiophene can be considered as a latent isoprene unit (bold lines).<sup>2</sup> Furthermore, substitution patterns of the type generalized in **B** are both exceedingly common in nature and frequently difficult to achieve using currently available techniques.<sup>3</sup>

Ring systems of type A have traditionally been prepared by electrophilic aromatic substitution processes, with only modest control in the introduction of groups R1 and R2, and little flexibility in the choice of substrates.<sup>4</sup> This represents a major drawback in the use of thiophenes in natural product synthesis. As an alternative approach, we were interested in the possibility that thiophenes of type **3** might be derived by an intramolecular Diels-Alder reaction of acctylenic thiazoles of general structure **1** (Scheme 1, following page). Although thiazoles are widely reported to be unreactive in 4 + 2 cycloadditions,<sup>5</sup> we have recently demonstrated that such reactions are feasible if proper geometrical constraints are imposed.<sup>6</sup> Finally, it was our hope that reductive modification of **3** might then provide the eremophilane-6-ones  $4\alpha$ , $\beta$  and/or the eremophilanes  $5\alpha$ , $\beta$ . Compound  $5\beta$  has found considerable importance in the correlation of absolute stereochemistry in the eremophilane class of sesquiterpenes.<sup>7</sup>



Scheme 1

In order to test this hypothesis we have developed a highly efficient route to the acetylenic thiazoles **1a**,**b** which can be routinely carried out on 0.5 g scales and larger (Scheme 2).<sup>8a</sup> Our initial experiments in this direction





## Scheme 2

were based upon a modified Schöllkopf reaction of the readily available thionolactone 7 with lithiomethylisocyanide (8a) (R = H).<sup>9</sup> It was anticipated that 8a would readily add to the highly electrophilic C=S bond in 7 to provide the 2-thiazoline anion 9a after intramolecular cyclization. Subsequent proton transfer and aromatization would then yield the desired thiazole alcohol 10a. Unfortunately, however, yields of 10a were disappointingly low following this direct procedure (< 25%), apparently due to competing proton abstraction at C-9. In contrast, the much less basic reagent 8b (R = tosyl) reacted smoothly with 7 to provide the thiazole alcohol 10b in 80% yield and with no competing side reactions. Once in hand, 10b could be cleanly converted to 10a by reductive cleavage with sodium amalgam in MeOH / THF (85 - 90%).<sup>10</sup> Both 10a and 10b were then carried on to the respective acetylenic ketones

1a and 1b by a sequence of reactions involving Swern oxidation to the aldehydes 11a and 11b (95%),<sup>11</sup> followed by condensation with lithiopropyne (88%), and re-oxidation (95%).

Not surprisingly, 1b was relatively unreactive in all attempts at conversion to the thiophene ketone 3, affording the desired material in only 10% yield after 21h at 350°C (Scheme 3). Under these same conditions,



 Decalin, 350°, 21h, 74% (R = H), 10% (R = Ts). ii. LAH / AlCl<sub>3</sub> (1:2), Et<sub>2</sub>O, RT, 79% ii. W-7 Ra-Ni, hexanes, 85%.

Scheme 3

however, we were pleased to find that 1a gave a 70 - 75% yield of 3, presumably due to the more electron rich nature of the thiazole ring. Furthermore, 3 could be cleanly reduced to the saturated analog 13, which on the basis of literature precedent was expected to be an ideal precursor for 7- $\alpha$ -eremophilane (5 $\alpha$ ).<sup>12</sup> This turned out not to be the case, however, since Raney-nickel cleavage of 13 consistently gave ~ 1 : 1 mixtures of 5 $\alpha$  and 5 $\beta$ , albeit in excellent overall yield.

Much more satisfactory results were obtained following the approach outlined in Scheme 4. Thus, 3 gave an



W-7 Ra-Ni, hexanes, 87% (> 95:5).
NaOMe / MeOH, 95-99% (> 98:2).
LAH, Et<sub>2</sub>O / THF, RT, 80-90%.
NaH, imidazole, CS<sub>2</sub>, Mel, THF, Δ, 80%.
K metal, t-BuNH<sub>2</sub>, 18-crown - 6, RT, 50%.

Scheme 4

85 - 90% yield of the isopropyl ketone  $4\alpha$ , contaminated with < 5% of the isomeric material  $4\beta$ , upon reductive cleavage with W-7 Raney nickel.<sup>13</sup> Compound  $4\alpha$ , in turn, could be quantitatively epimerized to the thermodynamically more stable  $4\beta$  upon equilibration with NaOMe / MeOH. Each of these materials was then carried on separately to the corresponding hydrocarbons  $5\alpha$  and  $5\beta$  by initial reduction to the  $\alpha$ -alcohols 14a,b (LAH, 80 -90%), followed by activation (80%) and cleavage according to the procedure of Barton *et al.* (> 80%, GC; 50% isolated,<sup>8b</sup> 4% recovered 14a,b).<sup>14</sup> The relative stereochemistry at C-6 for 14a and 14b was readily deduced from the H6 - H7 NMR coupling constants (J<sub>6,7</sub> = 2.3 Hz, 14a; J<sub>6,7</sub> = 9.9 Hz, 14b), and in addition, the NMR and IR spectra for  $5\beta$  were identical with those of an authentic sample.<sup>15</sup>

In closing, we believe that the described methodology could find considerable utility in the synthesis of related sesquiterpene ketones, alcohols, and hydrocarbons when more traditional methods of functionalization are impractical.<sup>16</sup>

## **References and Notes**

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8. (a) All yields refer to isolated and purified materials. All new compounds gave satisfactory elemental analyses and/or exact mass measurements, and were fully characterized by NMR, IR and mass spectroscopy. (b) The lower isolated yields in these examples are predominantly due to the somewhat volatile nature of  $5\alpha$  and  $5\beta$ .

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13. Models indicate that the difference in selectivity observed for the Ra-Ni reduction of 3 and 13 is a result of the fact that both possible chair conformations of 3 favor  $\beta$ -approach of the catalyst, while the two chair conformations of 13 exhibit opposite facial selectivity.

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