ORGANIC LETTERS

2003
Vol. 5, No. 3
325−328

A Concise Synthesis of the Tricyclic Skeleton of Pleuromutilin and a New Approach to Cycloheptenes

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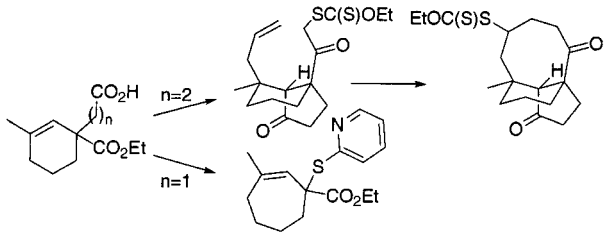
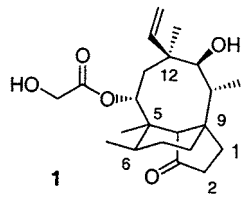
Received November 20, 2002

ABSTRACT



A short synthesis of the tricyclic skeleton of pleuromutilin is reported, featuring an unusually efficient 8-*endo*-trig radical cyclization of a xanthate precursor. In the course of this study, a one-carbon ring expansion leading to cycloheptenes was uncovered.

Pleuromutilin, **1**, and related derivatives are in current veterinary use as antimicrobials (Figure 1).[1] The unusual tricyclic structure, featuring a highly functionalized eight-membered ring straddling a hydrindanone core and nine contiguous stereogenic centers, has attracted the attention of several synthetic groups,[2] but despite much effort, only two total syntheses of Pleuromutilin have been completed so far.[2b,e]

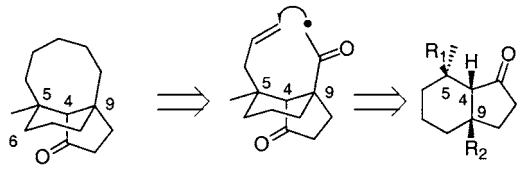


1

Figure 1. Pleuromutilin.

In view of the difficulties encountered by Paquette and co-workers while attempting to create the quaternary centers at C-5 and C-9 in later stages of the synthesis,[2d] we considered forming these centers early on and constructing the eight-membered ring by a direct radical cyclization, as shown by the retro-synthetic disconnection displayed in Scheme 1. To establish the viability of this approach, we embarked on the model studies described hereafter.

Scheme 1. Retrosynthetic Analysis



2 **3**

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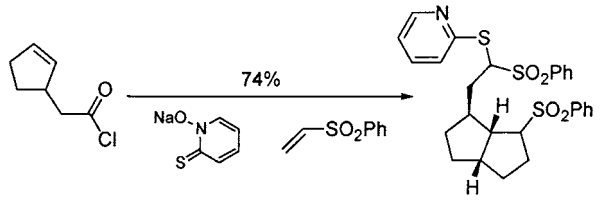
(1) For a review on the antibiotic activity of this class of compounds, see: Hunt, E. *Drugs Fut.* **2000**, *25*, 1163.

10.1021/ol027312m CCC: $25.00
Published on Web 01/08/2003

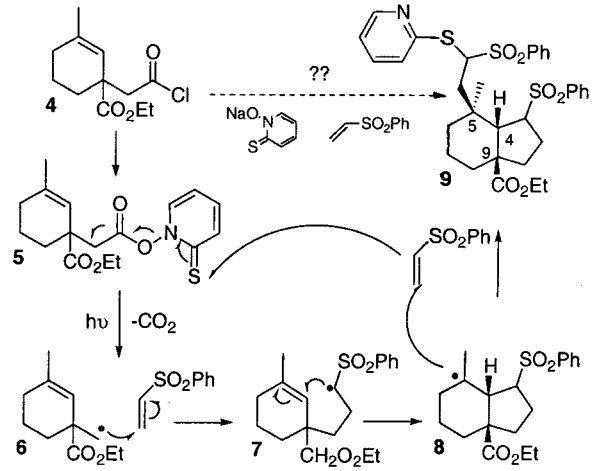
Scheme 2. An Early Radical Cascade



The hydrindanone framework **3** seemed accessible by a radical cascade, by analogy with a reaction we described some years ago and outlined in Scheme 2.[3]

Thus, starting from acid chloride **4** (Scheme 3), we hoped

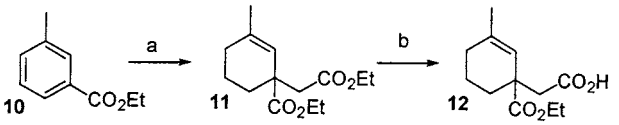
Scheme 3. Initial Synthetic Plan



that visible light irradiation of the Barton ester **5**, formed in situ, would generate primary radical **6** that would be captured by the electrophilic phenylvinyl sulfone trap. The radical adduct **7** would then undergo a 5-*exo*-trig ring-closure to give the *cis*-hydrindanyl radical **8**. A second addition to phenylvinyl sulfone, occurring from the least hindered *exo* face, would create the quaternary carbon at C-5 with the correct relative stereochemistry. The substitution pattern of the final product **9** would allow subsequent elaboration into the pleuromutilin skeleton, even though at this preliminary stage the methyl group on C-6 is lacking.

Carboxylic acid **12**, precursor of chloride **4**, was readily obtained from ethyl 3-methylbenzoate **10** as depicted in Scheme 4. Alkylative Birch reduction[4] followed by selective

Scheme 4. Synthesis of the Acid **12** Precursor of Acid Chloride **4**[a]

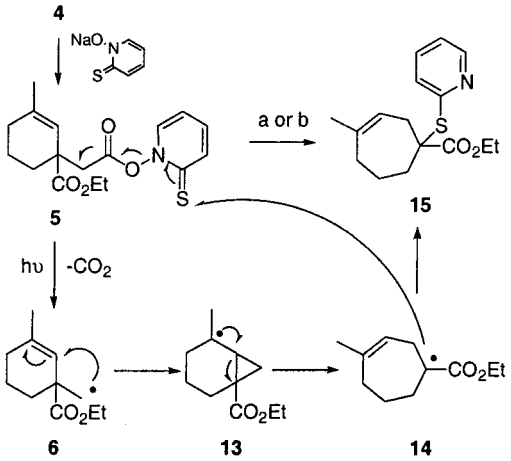


[a] Reagents and conditions: (a) (i) Li, NH_3 liq., *t*BuOH, THF, $BrCH_2CO_2Et$, (ii) H_2, $ClRh(PPh_3)_3$ cat. (80% 2 steps); (b) KOH, EtOH aq, +4 °C (75%).

hydrogenation of the least hindered olefin in the cyclohexadiene with Wilkinson's catalyst afforded cleanly diester **11**.[5] Finally, saponification under mild conditions allowed the regioselective cleavage of the more accessible primary ester providing acid **12** in good overall yield.

When the corresponding acid chloride **4** was gradually added to a refluxing mixture of phenylvinyl sulfone and the sodium salt of *N*-hydroxythiopyridone in cyclohexane under irradiation with a tungsten−halogen lamp, none of the expected adduct **9** could be isolated. Instead, compound **15** containing a cycloheptene ring was produced in 20% yield. This yield increased to 80% when the reaction was performed in the absence of the external trap. Clearly, ring expansion through bicyclo[4.1.0] radical **13** is faster than addition of radical **6** to phenylvinyl sulfone (Scheme 5).[6] This is

Scheme 5. An Unexpected Ring Expansion[a]



[a] Reagents and conditions: (a) phenylvinyl sulfone, CH_2Cl_2, rt, *hυ* (20%); (b) cyclohexane, reflux, *hυ* (80%).

presumably due to a Thorpe−Ingold effect speeding up the cyclopropane ring formation. The stabilized cycloheptenyl radical **14** generated by opening of the cyclopropyl ring propagates the radical chain, leading finally to the observed product.

(2) For previous studies concerning the total synthesis of pleuromutilin, see: (a) Kahn, M. *Tetrahedron Lett.* **1980**, *21*, 4547. (b) Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767 and references cited therein. (c) Patten, A. H.; Trost, B. M. *Diss. Abstr. Int.* **1987**, *47*, 3361-B; *Chem. Abstr. 106*, 156709. (d) Paquette, L. A.; Pansegrau, P. D.; Wiedeman, P. E.; Springer, J. P. *J. Org. Chem.* **1988**, *53*, 1461 and references cited therein. (e) Boeckman R. K., Jr.; Springer, D. M.; Alessi, T. R. *J. Am. Chem. Soc.* **1989**, *111*, 8284.

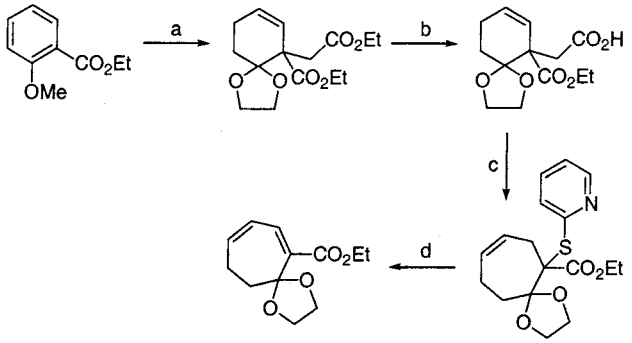
(3) Barton, D. H. R.; da Silva, E.; Zard, S. Z. *Chem. Commun.* **1988**, 285.

(4) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

(5) No selectivity in the reduction was observed with Pd/C; reduction with diimide was selective but the yield was poor.

(6) For a review on radical-based ring enlargements, see: Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

Scheme 6. Scope and Synthetic Potential[a]

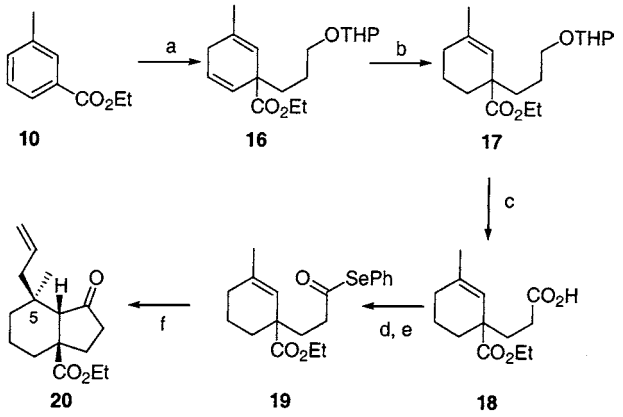


[a] Reagents and conditions: (a) (i) Li, NH_3 liq., *t*BuOH, THF, $BrCH_2CO_2Et$, (ii) $HOCH_2CH_2OH$, $BF_3{\cdot}Et_2O$, THF, rt. (55% 2 steps); (b) KOH, EtOH, reflux (95%); (c) (i) $(COCl)_2$, CH_2Cl_2, rt, (ii) sodium salt of *N*-hydroxy-2-thiopyridone, cyclohexane, reflux, *hν* (65% 2 steps); (d) (i) *m*CPBA, CH_2Cl_2, −78 °C, (ii) toluene, reflux (65% 2 steps).

Although the alternative pathway adopted by radical **6** frustrated our first approach to the hydrindanone structure, it represents nevertheless an interesting route to cycloheptenes since it combines the power of the alkylative Birch reduction with the mildness and flexibility of the Barton decarboxylation. The transformation shown in Scheme 6 gives an idea of its scope and synthetic potential.

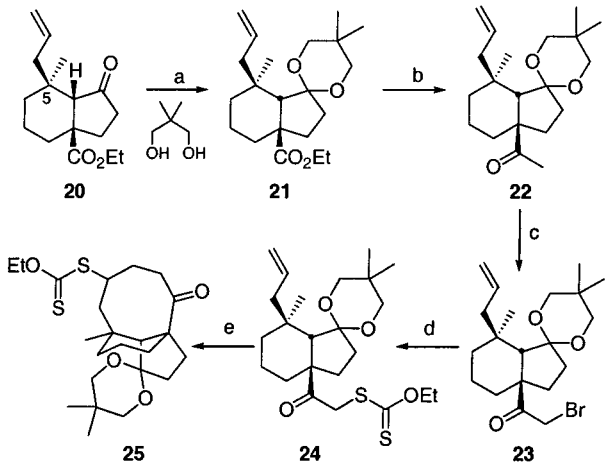
As for our synthesis of the hydrindanone portion of Pleuromutilin, it had to be redesigned in such a way that the radical intermediate would not be capable of undergoing the unwanted ring expansion. Once again, the alkylative Birch reduction was applied on ethyl *m*-toluate **10**, using THP-protected 3-bromopropanol as the alkylating agent, to give efficiently cylohexadiene **16**, whose disubstituted double bond was selectively reduced under the same conditions as above (Scheme 7). Oxidation of the resulting product **17** with

Scheme 7. Synthesis of Bicycle **15**[a]



[a] Reagents and conditions: (a) Li, NH_3 liq., *t*BuOH, THF, $Br(CH_2)_3OTHP$ (72%); (b) H_2, $ClRh(PPh_3)_3$ cat., rt (quantitative); (c) CrO_3, H_2SO_4, acetone, −10 °C (80%); (d) $(COCl)_2$, CH_2Cl_2, rt; (e) PhSeSePh, $NaBH_4$, EtOH 0 °C (75% 2 steps); (f) $AllylSnBu_3$, ACCN cat., heptane (55%).

Scheme 8. Construction of the Pleuromutilin Skeleton[a]



[a] Reagents and conditions: (a) PTSA, $HC(OEt)_3$, benzene, reflux (85%); (b) MeLi (5 equiv), THF, reflux (80%); (c) (i) LDA, TMSCl, THF, −78 °C, (ii) NBS, THF, $NaHCO_3$, −10 °C (80% 2 steps); (d) KSC(S)OEt, acetone, rt (quantitative); (e) DLP, 1,2-dichloroethane, reflux (60%).

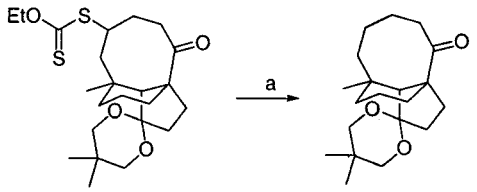
Jones reagent caused the deprotection of the alcohol and its oxidation to the corresponding carboxylic acid **18** in good yield. The derived acyl phenylselenide **19** was prepared by a standard procedure via the acid chloride. Heating this compound with allyltributyltin and a small amount of ACCN[7] in refluxing heptane furnished the desired hydrindanone **20** in 55% yield, along with 5% of the C-5 epimer (Pleuromutilin numbering). These two epimers result from a 5-*exo*-trig cyclization of the acyl radical followed by the trapping of the cyclized radical with allyltributyltin, mainly from the more accessible convex side of the bicyclic system.[8]

With a suitably functionalized hydrindanone in hand, the construction of the remaining ring in pleuromutilin skeleton was accomplished through the sequence displayed in Scheme 8. First the ketone group was protected as a ketal by using standard conditions and the hindered ester in **21** was then cleanly converted into methyl ketone **22** by treatment with excess methyllithium in refluxing THF. This is unusual behavior for an ester group, since no alcohol resulting from the *di*-addition of methyllithium was observed. It is possible that chelation of the lithium cation by the *β*-oxygen in the ketal group stabilizes the intermediate tetrahedral complex and prevents it from collapsing into ketone **22** before work up. This ketone, obtained in good overall yield, was then transformed into bromide **23** by exposure of its TMS enol ether to the action of *N*-bromosuccinimide. Displacement of the bromine with commercially available potassium *O*-ethyl xanthate proceeded uneventfully to give xanthate **24** in quantitative yield. We were delighted to find that this material smoothly underwent an 8-*endo*-trig cyclization when treated with a small amount of lauroyl peroxide in refluxing 1,2-dichloroethane. Compound **25**, possessing the tricyclic framework of Pleuromutilin, was isolated in 60% yield.

(7) ACCN: 1,1′-azobis(cyclohexanecarbonitrile). CAS registry number: 2094-98-6.

(8) For a review on acyl radicals see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

Scheme 9. Reductive Removal of the Xanthate Group[a]



25 **26**

[a] Reagents and conditions: (a) Bu_3SnH, AIBN cat., heptane, reflux (80%).

The direct formation of an eight-membered ring by a radical cyclization is relatively rare.[9] In contrast to most other radical-based methods, the xanthate technology does not generally suffer from the existence of major competing pathways that can irreversibly quench the intermediate radicals (for example, premature hydrogen abstraction from the stannane when using organotin hydrides).[10] The relatively long lifetime of the radicals in the medium allows intermolecular additions to unactivated olefins or ring closures that are otherwise troublesome, as in the present case of medium-size ring formation.[11]

The xanthate group in **25** provides a handle for introducing the remaing functionality present in Pleuromutilin, through the powerful and rich chemistry of sulfur. However, to further confirm the structure of **25**, the xanthate function was reductively removed by treatment with Bu_3SnH to give **26** in high yield (Scheme 9).

In summary, this study has uncovered a simple and flexible route to cycloheptenes based on the Barton decarboxylation reaction and demonstrated the possibility of using xanthate chemistry to build the eight-membered ring in Pleuromutilin. These encouraging preliminary results augur well for the synthesis of the natural product itself, which is currently under way.

Acknowledgment. We thank Thomas Tétart for participating in the ring expansion study as part of an undergraduate project and Aventis Pharma for generous financial support to one of us (F.P.).

Supporting Information Available: Detailed experimental procedures and spectra data for compounds **11**, **12**, and **15**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For a review on the use of free radical for the synthesis of medium size rings, see: Yet, L. *Tetrahedron* **1999**, *55*, 9349.

(10) For reviews on the chemistry of xanthates, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosph. Sulf. Silicon* **1999**, *153*−*154*, 137. (c) Zard, S. Z. *Radical in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2001, p 90. For other examples of 8-*endo*-trig radical cyclizations mediated by a xanthates, see: (d) Udding, J. H.; Giesselink, J. P. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 6671

(11) Interestingly, we have used xanthates to perform radical additions directly onto the vinyl group at C-12 of Pleuromutilin itself, *without prior protection of any of the functional groups*. See: Bacqué, E.; Pautrat, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2312.