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Total Synthesis of (+)-Pleuromutilin

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Abstract: The first enantiospecific total synthesis of the antibacterial natural product (+)-pleuromutilin has been achieved. The approach includes the synthesis of a non-racemic cyclisation substrate from (+)-*trans*-dihydrocarvone, a highly selective SmI_2-mediated cyclisation cascade, an electron transfer reduction of a hindered ester, and the first efficient conversion of (+)-mutilin to the target.

Keywords: natural products · pleuromutilin · radicals · samarium · total synthesis

Introduction

Resistance to antibiotics is a major global concern and new antibacterial agents with novel modes of action are urgently needed. The fungal secondary metabolite (+)-pleuromutilin (**1**) was first isolated in 1951 by Kavanagh and co-workers[1] and was found to display antibacterial activity through a novel mode of action involving binding to the prokaryotic ribosome (Figure 1).[2,3]

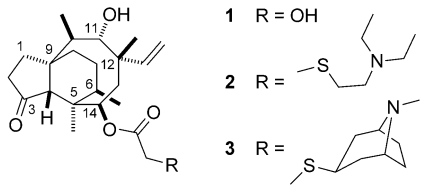
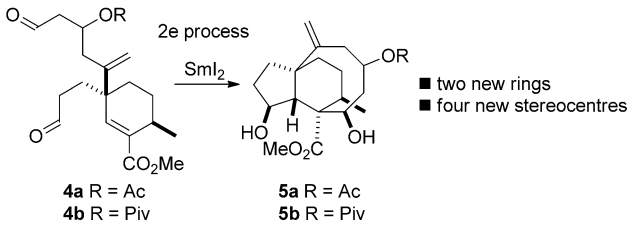


Figure 1. (+)-Pleuromutilin (**1**), tiamulin (Denegard®, **2**), retapamulin (Altabax®, **3**).

Analogues derived by semi-synthesis from pleuromutilin, including tiamulin (**2**; Denegard®) and retapamulin (**3**; Altabax®), are widely used. However, no orally bioavailable pleuromutilin antibiotic has been developed for use in humans.[3] Whilst semi-synthesis has provided useful analogues, pleuromutilins prepared by de novo synthesis have the potential to inform the design of a new generation of pleuromutilin-inspired antibiotics.

The structure of pleuromutilin presents a significant synthetic challenge: Gibbons[4] and Boeckman[5] have demonstrated impressive syntheses of racemic pleuromutilin, while Zard[6] and Sorensen[7] have reported elegant routes to the tricyclic core. The group of Sorensen has also assessed the bioactivity of the first totally synthetic analogues of pleuromutilin.[7b]

A SmI_2-mediated[8] cyclisation cascade reaction of dialdehydes[9] **4** lies at the heart of our approach to (+)-pleuromutilin. The cascade cyclisation generates tricyclic products **5** after assembly of both the 5- and 8-membered rings in a single step with high diastereocontrol at the four stereocentres formed during the reaction (Scheme 1).[10] The first total synthesis of (+)-pleuromutilin also features: 1) the development of a route to a non-racemic optimised substrate for the cyclisation cascade; 2) electron transfer reduction of a hindered ester during the manipulation of the cascade cyclisation product; 3) the first efficient conversion of mutilin into pleuromutilin.



Scheme 1. A SmI_2-mediated cyclisation cascade to construct the tricyclic core of (+)-pleuromutilin (Piv = pivaloyl).

Results and Discussion

Retrosynthetic analysis: Our retrosynthetic analysis of (+)-pleuromutilin is shown in Scheme 2. We envisaged installation of the quaternary centre at C12 and the hydroxyl at C11 by manipulation of the ketone in proposed intermediate **6**, which in turn could be prepared from cascade cyclisation products **5**. The major synthetic challenge in converting cascade products **5** into **6** is the reduction of the methyl ester at C5 to the methyl group present in the natural product. We proposed that dialdehyde cascade cyclisa-

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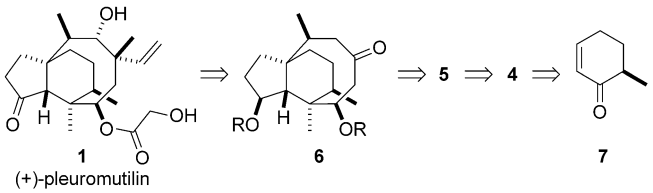
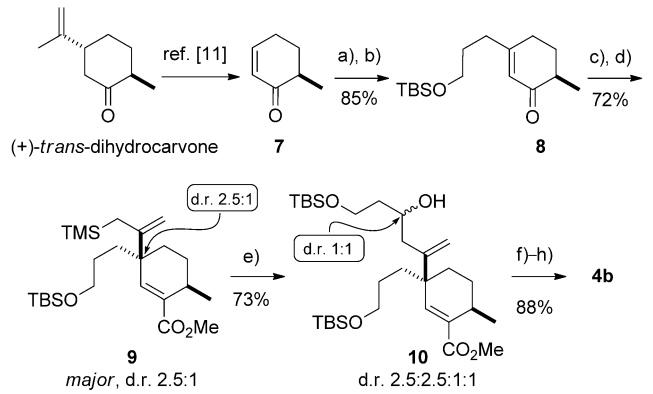


Scheme 2. Retrosynthetic analysis of (+)-pleuromutilin (**1**; R = protecting group).

tion substrates **4** would be accessible from (*R*)-6-methylcyclohex-2-enone (**7**), a member of the chiral pool.

Synthesis of the cascade cyclisation substrate: Dialdehyde cascade cyclisation substrate **4b** was prepared according to the procedure outlined in Scheme 3. Conjugate addition to

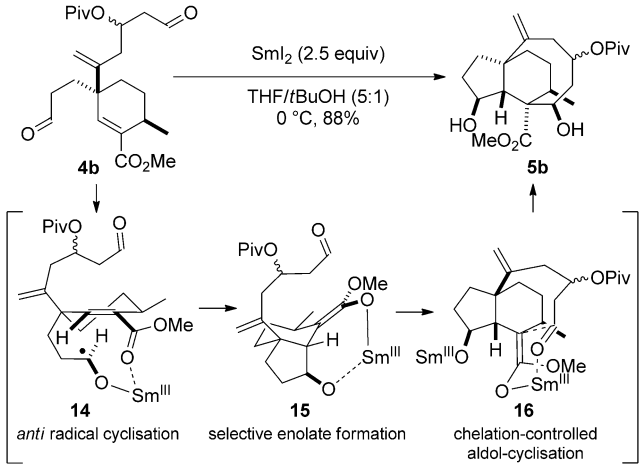


Scheme 3. Synthesis of the non-racemic cascade cyclisation substrate **4b**. Reagents and conditions: a) $TBSOCH_2CH_2CH_2MgBr$ (**11**), CuCN·2 LiCl, THF, −45 °C, 20 min; TMSCl, 10 min; **7**, 40 min; RT; b) $Pd(OAc)_2$ (10 mol %), DMSO, O_2, 3 days, 85 % (2 steps), 95 % *ee* by HPLC; c) CuI, $TMSCH_2C(MgBr)CH_2$ (**12**), THF, −78 to 0 °C, 10 min; **8**, −78 °C, 1.5 h; Comins' reagent, −78 °C to RT, 60 h, 85 %, 2.5:1 d.r.; d) $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF, CO, 40 °C, 24 h, 85 %. 2.5:1 d.r.; e) $TBSOCH_2CH_2CHO$ (**13**), $BF_3{\cdot}OEt_2$, TBAT, 4 Å MS, −78 °C, 18 h, −20 °C, 4 h, 73 %, 2.5:2.5:1:1 d.r.; f) PivCl, Py., DMAP, CH_2Cl_2, 18 h; g) HF, Py., MeCN, 0 °C to RT, 16 h; h) DMP, CH_2Cl_2, 3 h, 88 % (3 steps), 2.5:2.5:1:1 d.r.

7, obtained from (+)-*trans*-dihydrocarvone,[11] followed by catalytic Saegusa oxidation of the resultant TMS enol ether afforded **8** (95 % *ee*, chiral HPLC).[12] Addition of the organocopper reagent derived from Grignard **12**[13] to **8** proceeded with moderate diastereocontrol to give the corresponding vinyl triflate (2.5:1 d.r.) after trapping of the intermediate enolate with Comins' reagent.[14] Palladium-catalysed methoxycarbonylation then gave the α,β-unsaturated ester **9** in 85 % yield. Ester **9** was conveniently carried forward as a 2.5:1 mixture of diastereoisomers for separation at a later stage.

Lewis acid mediated addition of aldehyde **13**[15] to allylsilane **9** proceeded to give **10** in 73 % yield as an inconsequential 1:1 mixture of diastereoisomers at the newly formed centre.[16] Protection of the resultant secondary hydroxyl in **10** as the pivalate, followed by bis-desilylation and bis-oxidation using the Dess–Martin periodinane[17] gave the cascade cyclisation substrate **4b** in 88 % yield over 3 steps and as a 2.5:2.5:1:1 mixture of diastereoisomers.

SmI_2-mediated cyclisation cascade: Dialdehyde **4b** underwent efficient cascade cyclisation to give **5b** upon treatment with 2.5 equiv SmI_2 (Scheme 4). The choice of the pivalate



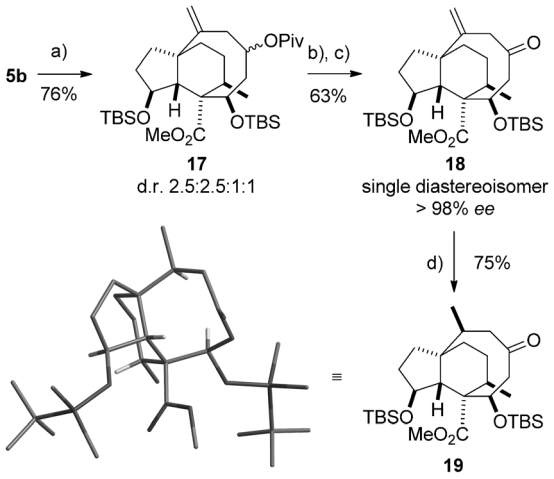
Scheme 4. Proposed mechanism for the SmI_2-mediated cyclisation cascade of **4b**.

protecting group for the secondary hydroxyl in **4b** proved significant: dialdehyde **4b** was more stable and easier to isolate than the analogous substrate bearing an acetate protecting group **4a**.

The cascade reaction is believed to commence with electron transfer to the left hand aldehyde in **4b** to give radical anion **14**, in which chelation between Sm^{III}, bound to the radical anion, and the carbonyl group of the ester controls the *anti*-5-*exo*-trig cyclisation[18] to form (after a second electron transfer) the (*Z*)-Sm^{III} enolate **15**.[19] The reaction cascade continues with aldol cyclisation of (*Z*)-Sm^{III} enolate **15** to give **5b**, via transition structure **16**. No by-products arising from "out of sequence" reduction were observed, and high diastereocontrol was achieved in the construction of the four contiguous stereocentres. Pre-coordination of samarium to the proximal aldehyde group and the ester carbonyl group may lead to its selective reduction over the more remote aldehyde. It is well-appreciated that pre-coordination of Lewis acidic samarium to the carbonyl group and unsaturated ester component in ketyl-olefin additions is important for promoting the reaction and controlling the diastereoselectivity of such additions.[20] Alternatively, reversible reduction of both aldehydes with one ketyl-radical anion being drained from the equilibrium through an efficient cyclisation may explain the apparent selectivity of aldehyde reduction.[21]

Following bis-silylation of the cascade cyclisation product **5b**, to give **17**, and removal of the pivalate, oxidation of the

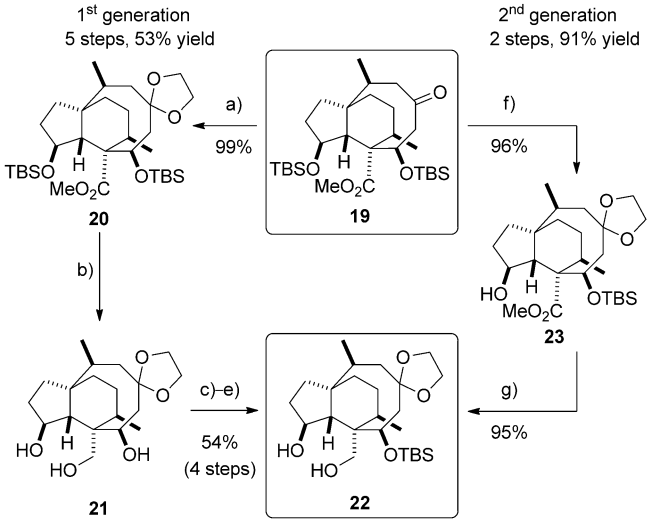
C12 hydroxyl gave a 2.5:1 mixture of ketones from which **18** was isolated as a single diastereoisomer in 63% yield (>98% *ee*, chiral HPLC; Scheme 5). Palladium-catalysed hydrogenation of **18** proceeded to give a 3:1 mixture of diastereoisomers at the newly formed stereocentre (C10). Ketone **19** was isolated as a single diastereoisomer in 75% yield (Scheme 5). The stereochemistry of **19** was determined by X-ray crystallographic analysis.[22]



Scheme 5. Manipulation of the cyclisation cascade product to give **19**. Reagents and conditions: a) Et_3N, TBSOTf, CH_2Cl_2, 0 °C, 5 min, RT, 30 min, 76%; b) $LiAlH_4$, Et_2O, 30 min; c) DMP, CH_2Cl_2, 16 h; major diastereoisomer isolated **18**, 63% (2 steps), >98% *ee* by HPLC; d) H_2, 10% Pd/C, EtOH, 12 h, 3:1 d.r.; major isomer **19** isolated in 75%.

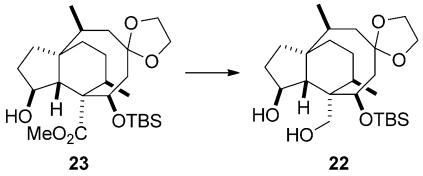
Reduction of the C5 methyl ester: With ketone **19** in hand, reduction of the methyl ester to the methyl substituent present at C5 in pleuromutilin was our next challenge. Protection of the ketone in **19** gave ketal **20** and subsequent treatment with $LiAlH_4$ at reflux in THF, led to reduction of the methyl ester with concomitant loss of both silyl protecting groups, to give unstable triol **21**. Fortunately, selective ketal formation allowed selective protection of the C3 hydroxyl and C5 hydroxymethyl groups. Protection of the C14 hydroxyl followed by ketal removal then gave diol **22** (Scheme 6).

In an attempt to avoid the protecting group manipulations needed to convert triol **21** to diol **22**, we sought a method for the selective reduction of the C5 ester. The use of excess Amberlyst® 15 in the ketal protection of **19** led to concomitant silyl deprotection, selectively at C3, to give **23** in 96% yield. Unfortunately, treatment of **23** with $LiAlH_4$ at room temperature, led to a mixture of reduction product **22** (21%), de-silylation product **21** (43%) and starting material **23** (34%; Table 1, entry 1). Our group has recently shown that SmI_2/amine/H_2O is a powerful reagent system for the reduction of simple esters,[23a] acids[23b] and lactones,[23c] and shows excellent tolerance of steric hindrance. Treatment of **23** with $SmI_2/Et_3N/H_2O$ led to ester reduction in 39% yield



Scheme 6. Reduction of the C5 methyl ester. Reagents and conditions: a) 1,2-ethanediol, $HC(OCH_3)_3$, Amberlyst® 15 (catalytic), toluene, MeCN, RT, 18 h, 99%; b) $LiAlH_4$, THF, reflux, 20 h; c) 2,2-dimethoxypropane, CSA, RT, 5 min; d) TBSOTf, DMAP, Et_3N, CH_2Cl_2, RT, 30 min; e) PPTS, EtOH, RT, 48 h, 54% (4 steps); f) 1,2-ethanediol, $HC(OCH_3)_3$, Amberlyst® 15 (5 equiv), PhMe, MeCN, RT, 40 h, 96%; g) SmI_2/amine/H_2O, see Table 1.

Table 1. Optimisation of ester reduction.

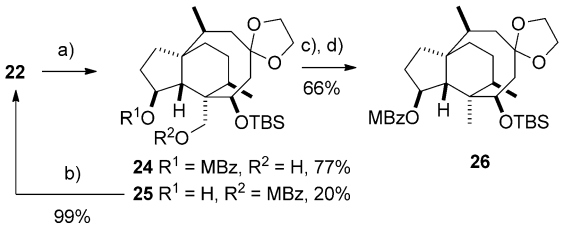


Entry	Reductant	**22**[a] [%]	**21**[a] [%]	Yield [%]
1	$LiAlH_4$[b]	21	43	–
2	$SmI_2/Et_3N/H_2O$[c]	40	–	39[d]
3	$SmI_2/Et_3N/H_2O$[e]	92[f]	–	90
4	SmI_2/pyrrolidine/H_2O[e]	>95	–	95
5	SmI_2/HMPA/H_2O	<5	–	–

[a] Determined by ^1H NMR spectroscopy. [b] $LiAlH_4$ (10 equiv), THF, RT, 18 h. [c] SmI_2 (20 equiv)/Et_3N/H_2O (1:6:3), THF, RT, 18 h. [d] 98% brsm. [e] SmI_2 (20 equiv)/amine/H_2O (1:3:3), THF, RT, 18 h. [f] After two re-treatments of the crude product mixture.

with 60% recovery of starting material (Table 1, entry 2). The crude mixture from the $SmI_2/Et_3N/H_2O$ reduction could be retreated under the same conditions and after three iterations, 92% conversion was achieved and diol **22** was isolated in 90% yield (Table 1, entry 3). The use of pyrrolidine as the amine component in the reagent system has been shown to give a more powerful reductant for the reduction of hindered esters.[23a] Pleasingly, the use of SmI_2/pyrrolidine/H_2O gave near complete conversion in the reduction of **23** and a 95% yield of **22** (Table 1, entry 4). Interestingly, the use of HMPA, a classical additive for promoting the reactivity of SmI_2,[8f] led to no conversion (Table 1, entry 5). Attempted use of the alternative electron transfer reagent, Na/SiO_2,[24] for the reduction of **23** returned only starting material.

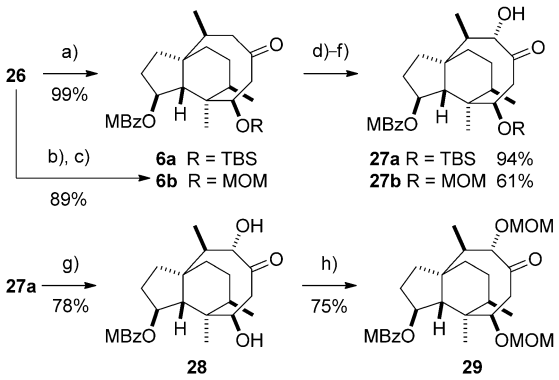
The second generation approach for the conversion of **19** to diol **22** is three steps shorter than our original route, does not involve formation of the unstable triol **21**, and is considerably higher-yielding. Protection of the C3-hydroxyl in diol **22** as the *p*-methylbenzoate (MBz) gave **24** in 77% yield. Primary MBz ester **25** was also obtained in 20% and could be efficiently recycled to the diol **22** by hydrolysis. Conversion of **24** to the corresponding thioimidazolide proceeded in 67% yield.[25] The desired primary thioimidazolide was deoxygenated under radical conditions[26] to give **26** in 99% yield (Scheme 7).



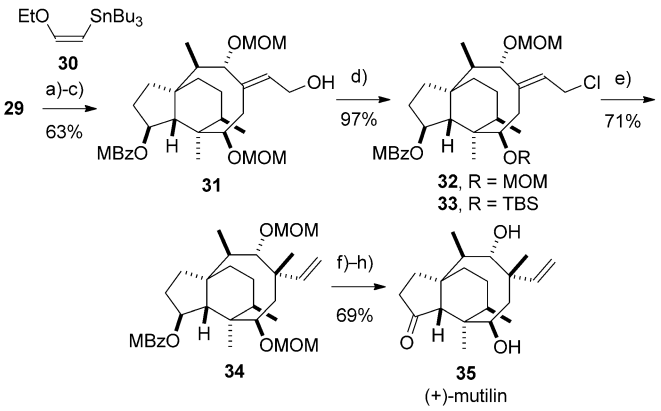
Scheme 7. Deoxygenation of the C5 hydroxymethyl group. Reagents and conditions: a) LDA, −78 °C, 30 min; MBzCl, THF, −78 °C, 30 min, 97%; b) NaOMe, MeOH, RT, 24 h, 99%; c) TCDI, THF, 60 °C, 5 days; d) nBu$_3$SnH, AIBN, PhMe, 80 °C, 4 h, 66% (2 steps).

Elaboration of the eight-membered ring: We next examined the functionalisation of the eight-membered ring in **26**. The ketone at C12 was revealed by deprotection of **26** to form **6a**.[27] The procedure of Boeckman was used for the selective α-hydroxylation of **6a**:[5] formation of the silyl enol ether of **6a**, followed by epoxidation, rearrangement and treatment with TBAF gave the α-hydroxy ketone **27a** in 94% yield with complete regio- and diastereocontrol. The relative stereochemistry of **27a** was determined by NOE analysis on a related compound (see the Supporting Information). Interestingly, Rubottom oxidation of MOM ether **6b** under the same conditions proceeded with lower diastereocontrol and gave **27b** in only 61%, a result in accord with that reported by Boeckman.[5] Thus, the nature of the C14 substituent, clearly has a large impact on the selectivity of this oxidation step. Conversion of **27a** to the bis-MOM ketone **29** is shown in Scheme 8.

Building on the findings of Gibbons and Boeckman, we envisaged installing the C12 quaternary stereocentre by S_N2' displacement of an allylic leaving group; the allylic alcohol **31** was prepared by modifying the procedure of Gibbons. Ketone **29** was treated with the lithiated enol ether formed from the stannane **30**,[28] the addition product was hydrolysed[27] and the intermediate enal was reduced[29] to give allylic alcohol **31** in 63% overall yield. Subsequent Corey–Kim chlorination[30] proceeded in high yield to give allylic chloride **32**, a compound similar to the allylic chloride used in Boeckman's synthesis (Scheme 9). Pleasingly, S_N2' alkylation of **32** using Me_2Zn and CuCN in DMF[31] proceeded in 71% yield to give **34** as a single diastereoisomer at C12. The S_N2' alkylation of allylic chlorides with organocopper and organozinc reagents can proceed with high levels of 1,2-diastereocontrol. In particular, the presence of an α-OMOM substituent, generally favours formation of the 1,2-*anti*-product as is observed in the conversion of **32** into **34**.[32] Interestingly, analogous TBS (*tert*-butyldimethylsilyl) protected allylic chloride **33**, did not undergo S_N2' alkylation under a range of conditions. We believe this is due to the increased steric hindrance at C12 when there is a bulky OTBS group at C14. Removal of the MBz group from **34** followed by Dess–Martin oxidation and MOM deprotection gave (+)-mutilin **35** in 69% overall yield. Synthetic **35** was identical to natural material (Scheme 9).



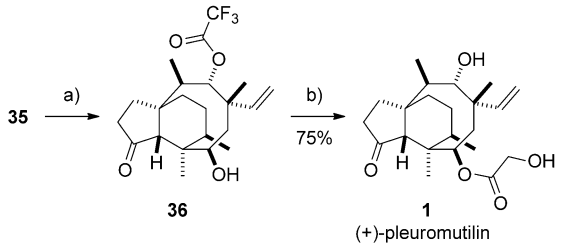
Scheme 8. Synthesis of **29**. Reagents and conditions: a) $FeCl_3$·SiO_2, acetone, RT, 24 h, **26**–**6a** 99%; b) HF, MeCN, H_2O, RT, 16 h; c) MOMCl, DIPEA, CH_2Cl_2, RT, 24 h, 89% (2 steps); d) HMDS, TMSI, CH_2Cl_2, −20 to 10 °C, 3 h; e) $NaHCO_3$, *m*CPBA, CH_2Cl_2, 0 °C, 10 min; f) TBAF, THF, RT, 3 min, **6a**–**27a** 94%, **6b**–**27b** 61% (3 steps); g) $HF_{(aq.)}$, MeCN, RT, 18 h, 78%; h) MOMCl, DIPEA (3 additions), CH_2Cl_2, RT, 2 days, 75%.



Scheme 9. Synthesis of (+)-mutilin (**35**): Reagents and conditions: a) **30**, *n*BuLi, THF, −78 °C, 1 h; **29**, THF, −78 °C, 15 min; b) $FeCl_3$·SiO_2, acetone, RT, 5 min; c) $NaBH_4$, THF/H_2O, RT, 30 min, 63% (3 steps); d) NCS, DMS, CH_2Cl_2, 0 °C, 10 min, **31**, −20 °C to RT, 16 h, 97%; e) CuCN, DMF, RT, 30 min, Me_2Zn, −20 °C, 24 h, 71%; f) $LiAlH_4$, THF, RT, 90 min; g) DMP, CH_2Cl_2, RT, 1 h; h) AcCl, EtOH, RT, 3 h, 69% (3 steps).

Existing methods for the conversion of mutilin to pleuromutilin suffer from poor selectivity and yields.[4c,5b] Adaption

of a method developed in industry for the conversion of mutilin to C14 analogues of pleuromutilin[33] allowed us to address this problem. Selective conversion of (+)-mutilin (**35**) to the C10 trifluoroacetate **36** was followed by coupling with 2-(2,2,2-trifluoroacetoxy) acetic acid. Subsequent deprotection then gave (+)-pleuromutilin (**1**) in 75% overall yield (Scheme 10). The ^{1}H NMR, ^{13}C NMR, IR spectra, optical rotation, HRMS and melting point for synthetic **1** were in full accord with the literature (see the Supporting Information).



Scheme 10. Conversion of (+)-mutilin to (+)-pleuromutilin. Reagents and conditions: a) trifluoroacetylimidazole, EtOAc, −45 °C, 30 min; b) 2-(2,2,2-trifluoroacetoxy)acetic acid, EDCI, DMAP, CH_2Cl_2, RT, 30 min; MeOH, Et_3N, 24 h, 75% (2 steps).

Conclusion

We have achieved the first enantiospecific total synthesis of (+)-pleuromutilin. (+)-*trans*-Dihydrocarvone was used to synthesise an optimised substrate for a SmI_2-mediated dialdehyde cyclisation cascade that constructs the pleuromutilin core with high diastereocontrol. Electron transfer reduction of a sterically hindered ester was the key step in the successful manipulation of the cascade cyclisation product. Finally, an efficient method for the conversion of mutilin to the target has been developed. Our approach is currently being used to expand the pleuromutilin class of antibiotics through the synthesis of novel analogues that are inaccessible from the natural product.

Experimental Section

The synthesis and characterisation of the compounds studied in this manuscript can be found in the Supporting Information.

Acknowledgements

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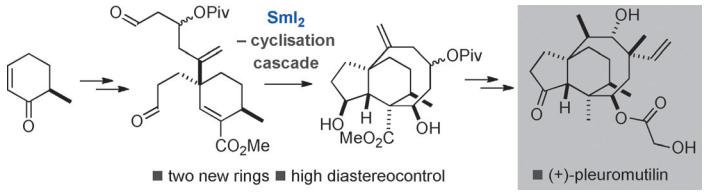

Two-electron cyclisation cascade: The first enantiospecific total synthesis of the antibacterial (+)-pleuromutilin has been achieved. The approach includes the synthesis of a non-racemic cyclisation substrate from (+)-*trans*-dihydrocarvone, a highly selective SmI_2-mediated cyclisation cascade, an electron transfer reduction of a hindered ester, and the first efficient conversion of (+)-mutilin to the target (see scheme; Piv = pivaloyl).

Total Synthesis

*N. J. Fazakerley, M. D. Helm, D. J. Procter** ..... ■■■■–■■■■

Total Synthesis of (+)-Pleuromutilin

The first enantiospecific total synthesis…
…of (+)-pleuromutilin is reported. A SmI_2-mediated cyclisation cascade allows access to the tricyclic core of the antibacterial natural product, constructing the five- and eight-membered rings in a single step, with high diastereocontrol. For more details, see the Full Paper by D. J. Procter et al. on page ■■ ff.