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A NEW SYNTHETIC ROUTE TO (±)-THIENAMYCIN VIA 4-*EXO* TRIGONAL CYCLISATION OF CARBAMOYL COBALT INTERMEDIATES

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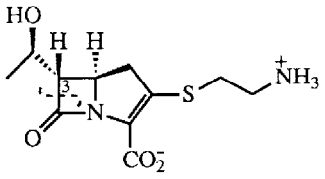
Summary: A new synthesis of (±)-thienamycin (1), based on elaboration of the key intermediate (12) in one step by heating a solution of the carbamoylcobalt salophen (11) in toluene, is described.

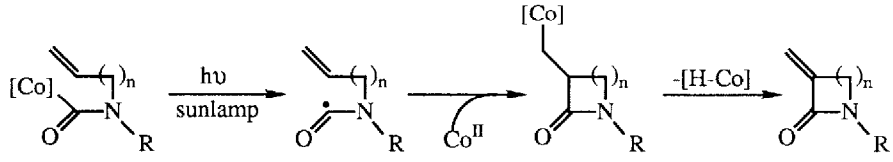
Since the publication of its presence in the fermentation broths of *Streptomyces cattleya* during 1976,[1] the novel antibiotic thienamycin (1) has been at the focal point of many innovative and ingenious synthetic studies.[2,3] A synthetic design to the β-lactam moiety in (1) that has received little attention however is one which uses a cyclisation reaction involving the amide carbonyl and C-3 in an acyclic precursor molecule *i.e.* disconnection shown in Formula 1.[4] In contemporaneous studies, we have described the synthesis of several unsaturated carbamoylcobalt reagents (2) and illustrated their potential as precursors to carbamoyl radical intermediates *viz* (3), upon heating or simple irradiation with a conventional sunlamp.[5] Furthermore, we have demonstrated that under appropriate conditions, the intermediates (3) undergo facile cyclisation accompanied by trapping (*e.g.* with Co^{II} or TEMPO) or dehydrocobaltation leading to functionalised β-, γ- or δ- lactams (4) (Scheme 1). In this *Letter* we show how this chemistry has now been developed to provide a new synthetic route to thienamycin (1).



(1)

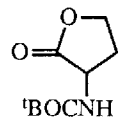
The key feature in our strategy towards thienamycin was the regio- and stereoselective 4-*exo* trigonal cyclisation of the substituted N-allylcarbamoylcobalt (11) to the *trans*-substituted azetidin-2-one intermediate (12). The carbamoylcobalt(III) salophen (11) was prepared first therefore, starting from N-^{t}BOC protected (±)-α-amino-γ-butyrolactone (5). Thus, reduction of (5) with DIBAL-H (CH_2Cl_2, -78°C, 0.25h) provided the corresponding lactol (6; 83%) which was then converted into the substituted allylamine (7; 54%) by Wittig condensation with *i*-Pr $Ph_3P^+Br^-$ ($NaNH_2$, CH_2Cl_2, C_6H_5Me, 70°C, 1h). Treatment of (7) with two equivalents of NaH and benzyl bromide next led to the *bis*-benzyl derivative (8), which could be converted into the free amine (9) following reaction with pTSA and aqueous base work-up.[6] Acylation

of (9) with triphosgene (C_5H_5N - C_6H_6, 25°C, 96h) followed by treatment of the resulting carbamoyl chloride (10) with sodium cobalt salophen reagent[5] (THF, N_2) finally provided (35% over two steps) the carbamoylcobalt salophen (11) as red crystals, m.p. 142-52°C (decomp.).[7]

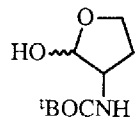


Scheme 1

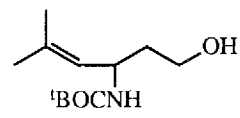
When a solution of the carbamoylcobalt (11) in toluene was heated under reflux in an atmosphere of N_2 for 24h, it underwent sequential homolytic cleavage, cyclisation (4-*exo*-trig) and dehydrocobaltation producing exclusively the *trans*-disubstituted azetidin-2-one (12) in 40% overall yields.[8] Oxidative cleavage of the propenyl side chain in (12) in the presence of ozone (CH_2Cl_2, -78°C, 3 min.)[4] next led to the corresponding ketone (13; 82%) which then underwent stereoselective reduction[4,9] using K-selectride-KI in THF to provide the *trans*-4-(2'-benzyloxyethyl)-3-(1'-hydroxyethyl)-N-benzylazetidin-2-one (14). The azetidin-2-one (14) has been converted in three steps into the bicyclic molecule (15)[10] which is the key intermediate in the synthesis of thienamycin (1) described by Merck and Co.[2b] Our new strategy for the synthesis of the azetidin-2-one (14) based on the disconnection shown in Formula 1, therefore constitutes a new formal synthesis of thienamycin.



(5)



(6)



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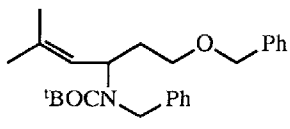

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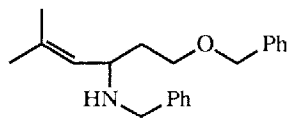

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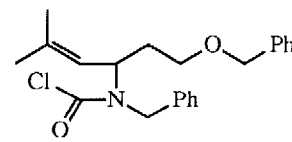
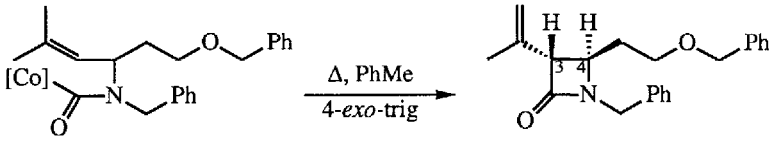
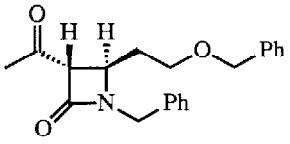


(10)



(11) (12)

[Co] = cobalt (III) salophen



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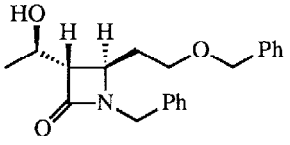
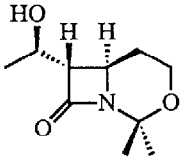


(14)



(15)

Acknowledgements

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3. See P.A.Grieco, D.L.Flynn and R.E.Zelle, *J.Am.Chem.Soc.*, **1984**, *106*, 6414 and references cited therein. For reviews, see: T.Kametani, *Heterocycles*, **1982**, *17*, 463, and T.Nagahara and T.Kametani, *Heterocycles*, **1987**, *25*, 729.
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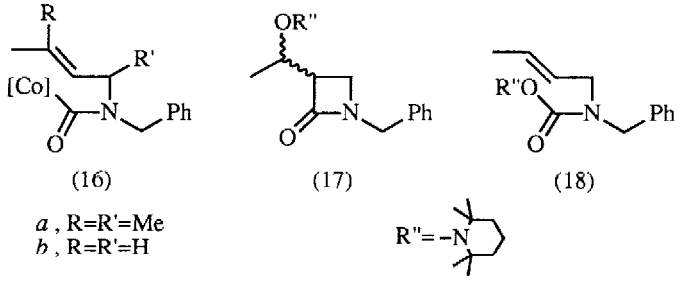
7. Satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data were obtained for all new compounds. The substituted allylamine (7) showed ν_{max} 3340, 2977, 2930, 1690 cm.$^{-1}$, δ_H 5.0 (app. dquint., *J*8.4 and 1.3 Hz, : C*H*), 4.6 (br, NH), 4.5 (m, CH), 3.6 (br, OCH_2), 3.5 (OH), 1.75 (m, C*H*H), 1.7 (d, *J* 1.3 Hz, : CMe), 1.68 (d, *J* 1Hz, : CMe), 1.45 (m, CH*H*), 1.4 (CMe_3) p.p.m. whereas the carbamoylcobalt salophen (11) had λ_{max} 256 (21,350), 300 (11,200) 370 (9,300) nm., ν_{max} 1610, 1580 cm.$^{-1}$, δ_H 8.7 (2 x HC : NR), 7.9 (m, 2 x ArH), 7.4-6.6 (m, 20 x ArH), 5.8 (d, *J* 15.6 Hz, NC*H*H), 4.9 (d, *J* 9 Hz, : C*H*), 4.7 (d, *J* 15.9 Hz, NCH*H*), 4.3 (m, NH), 4.0 (d, *J* 11.8 Hz, OC*H*HAr), 3.95 (d, *J* 11.9 Hz, OCH*H*Ar), 2.75 (m, OCH_2) 1.55 (m, CH_2), 1.2 (Me), 0.7 (Me). The carbinol (14) was secured as a 5:1 mixture of β- and α- OH epimers with the major β-epimer drawn showing ν_{max} 3420, 3030, 2930, 1730 cm.$^{-1}$, δ_H 7.25 (m, 10 x ArH), 4.5 (d, *J* 15.4 Hz, NC*H*H), 4.35 (OCH_2 Ar), 4.05 (d, *J* 15.4 Hz, NCH*H*Ar), 4.0 (dq, *J* 7.4 and 6.3 Hz, C*H*OH), 3.5 (ddd, *J* 9.3, 4.0 and 2.0 Hz, 4-CH), 3.4 (app. t, *J* 6.2 Hz, OCH_2), 2.9 (dd, *J* 7.4 and 2.0 Hz, 3-CH), 2.6 - 2.3 (OH), 1.9 (m, C*H*H), 1.6 (m, CH*H*), and 1.2 (d, *J* 6.3 Hz, CH_3); δ_C 167.6, 137.6, 135.9, 128.5, 128.2, 127.9, 127.4, 72.9, 66.8, 65.8, 62.1, 53.3, 44.3, 31.2, 21.2 p.p.m.

8. The *trans*-stereochemistry of the azetidin-2-one (12) followed conclusively from the magnitude of the vicinal coupling ($J_{3,4}$ 2.2 Hz) between C-3-H and C-4-H in the p.m.r. spectrum of (12); *cf*. $J_{3,4}$ 5.9 Hz for the corresponding *cis*-stereochemistry.[4] The 4-*exo*-trig cyclisation of N-allylcarbamoylcobalt intermediates was initially modelled with a range of substrates, including (16*a*) and the 'crotyl' derivative (16*b*). Each model compound produced only the corresponding *trans*-azetidin-2-one product. In an attempt to introduce oxygenation in the side chain of the azetidinone in tandem with cyclisation, the 'crotyl' derivative (16*b*) was heated with TEMPO, under the usual conditions.[5] Unfortunately only trace amounts of the azetidinone (17) were secured by this procedure, the major product being the adduct (18).



(16) (17) (18)

a, R=R'=Me
b, R=R'=H

R"= -N

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