Total Synthesis of (−)-4a,5-Dihydrostreptazolin

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(−)-4a,5-Dihydrostreptazolin has been synthesized in nine steps from D-glyceraldehyde acetonide. Key steps include a diastereoselective addition of a vinylic Grignard reagent to an imine derived from D-glyceraldehyde acetonide, a ring-closing metathesis, and a stereoselective radical-mediated enyne cyclization.

Introduction

(+)-Streptazolin, first isolated from cultures of *Streptomyces viridochromogenes* in 1981, was found to exhibit antibiotic and antifungal properties.[1,2] The pure compound is rather labile, due to the presence of the conjugated diene part, which enhances its polymerization, although it may be kept for some time in dilute solutions at low temperature. Most structural investigations have therefore been carried out on a derivative, (+)-5,8-dihydrostreptazolin acetate, obtained by catalytic hydrogenation and acetylation of streptazolin. Although less active, this derivative also exhibits antibacterial activity (Figure 1).[3]

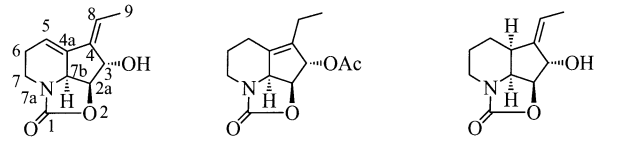

Figure 1. (+)-Streptazolin and derivatives

The unique structure of streptazolin has elicited some synthetic interest, and four total syntheses have been achieved. The first racemic one, by Kozikowski, features an aza-Ferrier reaction and a [3 + 2] nitrile oxide-alkene cycloaddition to construct the azabicyclic core of streptazolin.[4] The ethylidene side-chain was installed by means of a Wittig reaction, which took place with low stereoselectivity and afforded streptazolin as a mixture of geometrical isomers. Two enantioselective syntheses were subsequently carried out. Both started from an L-tartaric acid derivative, the absolute configuration of which translates directly to the C-2a and C-3 stereocenters.[5,6] Both approaches rely on a vinylsilane−iminium cyclization for the construction of the tetrahydropyridine ring. In Overman's approach,[5] the five-membered ring was elaborated by an intramolecular acylation of a vinylic organolithium reagent, producing an azabicyclic ketone that had previously been synthesized in racemic form.[4b] In Kibayashi's approach, a palladium-catalyzed enyne cycloisomerization allowed direct stereoselective access to (+)-streptazolin for the first time.[6] More recently, Comins reported the first chiral-auxiliary-mediated synthesis of (+)-streptazolin, starting from an *N*-acylpyridinium salt.[7]

Since streptazolin does not obviously meet the criteria for an ideal antibiotic, owing to its marginal activity and its low stability, attempts were made to synthesize derivatives with improved properties.[8,9] Recently, 5-(alk-1-enyl)-1,2,3,6-tetrahydropyridines, mimicking only the two suggested pharmacophores of streptazolin (the diene and the carbamate moieties), have been synthesized, but despite their enhanced stability, no satisfactory improvement in the antibiotic activity was observed.[10] These studies have highlighted the possible importance of the five-membered ring and probably its alcohol functionality at C-3. We were particularly interested in another dihydro derivative of streptazolin, (−)-4a,5-dihydrostreptazolin (Figure 1), which is structurally closely related to streptazolin thanks to the presence of the exocyclic alkene moiety, but which has not, to the best of our knowledge, been evaluated for biological activity. One synthesis of (−)-4a,5-dihydrostreptazolin has already been described by Kibayashi, taking advantage of the same enyne intermediate as involved in the synthesis of streptazolin, and carrying out the palladium-catalyzed enyne cycloisomerization in the presence of a reducing agent.[11] In order to assess the biological properties of this structurally interesting compound, we have achieved its total synthesis[12] and prepared some related structures. Here we would like to give a full account of this work.

Results and Discussion

In our retrosynthetic analysis of (−)-4a,5-dihydrostreptazolin, we anticipated that a radical-mediated enyne cyclization induced by nBu$_3$SnH[13] could be used in order to elaborate the five-membered ring. This reaction would produce a vinylstannane as a reasonable precursor to the target, offering potential control over the exocyclic double bond configuration and the *cis*-fused ring junction. Two different approaches for the preparation of the enyne precursor were considered. In the first approach (Path A), we envisaged

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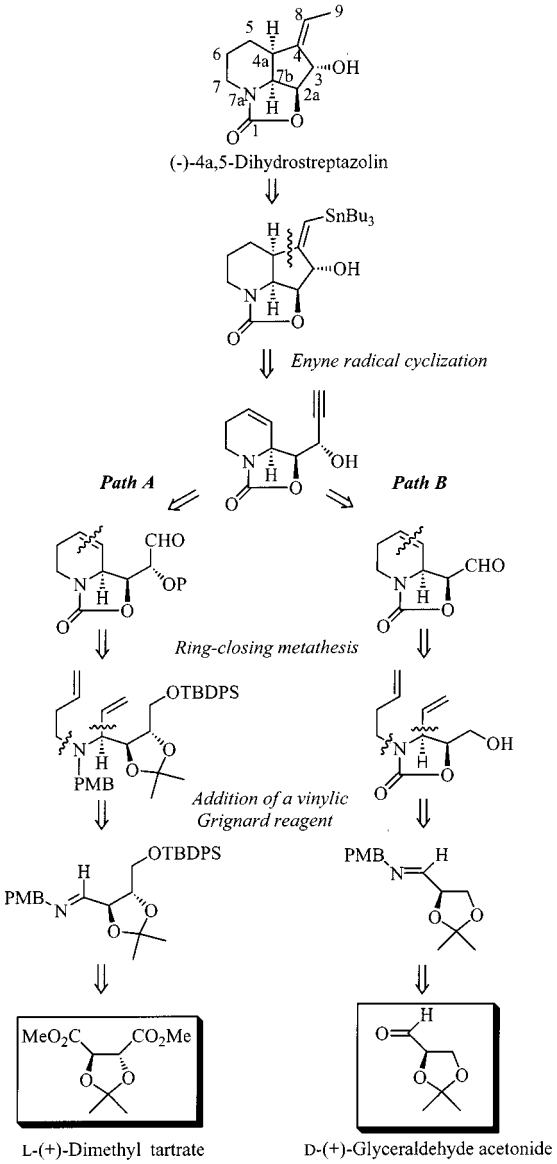
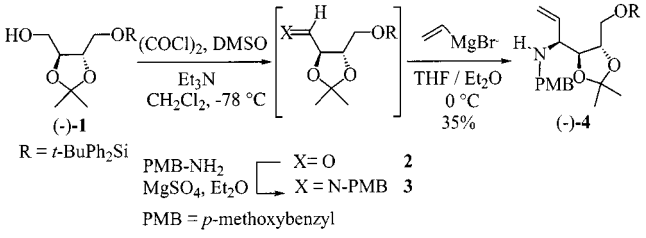
introducing the triple bond by performing a Fuchs−Corey[14a] or a Seyferth−Gilbert[14b,14c] reaction on the corresponding aldehyde. This strategy, as in the previously reported total syntheses of streptazolin, would take advantage of the possibility of using L-tartaric acid derivatives to introduce the C-2a and C-3 stereocenters.[5,6] We envisaged that the tetrahydropyridine ring could be formed by ring-closing metathesis of the corresponding diene,[15] for which the homoallyl substituent would be introduced by alkylation of the nitrogen, and the vinyl group by addition of a vinylic Grignard reagent to the corresponding imine (Scheme 1).



Scheme 1. Retrosynthetic analyses for (−)-4a,5-dihydrostreptazolin

A second shorter approach (Path B) involved the introduction of the triple bond by addition of an acetylenic Grignard reagent to the corresponding aldehyde. We anticipated that the diastereoselectivity of this nucleophilic addition to the chiral α-oxygenated aldehyde would easily be controllable by variation of the experimental conditions,[16] thus also allowing easy access to both C-3 epimeric compounds. The aldehyde would be produced from the corresponding alcohol by oxidation and the tetrahydropyridine ring would be elaborated by a ring-closing metathesis,[15] in an approach similar to that described above. In this case, D-glyceraldehyde acetonide was selected as an optically active starting material, while addition of the Grignard reagent to the corresponding imine would dictate the absolute configuration at C-7b in both approaches (Scheme 1).

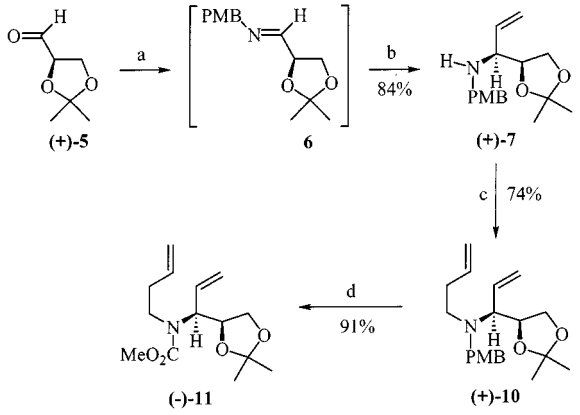
The initial stages of Path A were examined first. The known alcohol (−)-**1**, prepared in three steps from L-dimethyl tartrate (acetonide formation, $LiAlH_4$ reduction, and monosilylation with NaH/TBDPSCl, 64% overall yield),[17] was oxidized to afford the unstable aldehyde **2**, which was converted directly into the imine **3** by treatment with *p*-methoxybenzylamine (PMB-NH_2) in the presence of anhydrous $MgSO_4$. Although Grignard reagents were reported to be unreactive towards such imines in the absence of additives,[18] treatment of **3** with vinylmagnesium bromide afforded the allylic amine **4** in modest overall yield (35%, *dr* ≥ 95:5). Its relative configuration was not determined, but was assumed to be *anti* on the basis of literature precedent for this series of compounds.[18−20] Although this route would have unambiguously ensured the absolute configurations at C-2a and C-3, it was abandoned because of the low yields of the first steps and the greater number of functional group manipulation steps required in comparison with Path B (Scheme 2).



Scheme 2. Synthesis of allylic amine (−)-**4** according to Path A

Following the second approach (Path B), D-glyceraldehyde acetonide (+)-**5**, readily prepared by oxidative cleavage of 1,2,5,6-diisopropylidene-D-mannitol,[21] was converted into imine **6** by treatment with *p*-methoxybenzylamine in the presence of anhydrous $MgSO_4$ in ether. This was then allowed to react directly with vinylmagnesium chloride, to afford the allylic amine (+)-**7** (84%) in a highly diastereoselective fashion (*dr* ≥ 98:2) (Scheme 3).

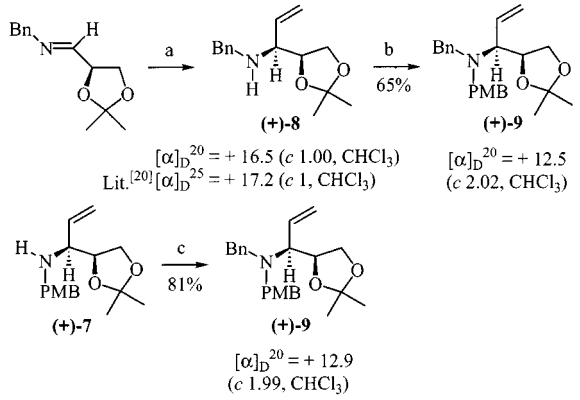
Although the addition of vinylmagnesium bromide to the benzylimine of D-glyceraldehyde has already been studied and shown to afford the corresponding allylic amine (+)-**8** without racemization,[20] we nevertheless checked that the same result was obtained in our hands during the alkylation of **6** with vinylmagnesium chloride. Thus, optically pure (+)-**8** was prepared as described[20] and alkylated with *p*-methoxybenzyl bromide to afford the tertiary amine (+)-**9** (65%). At the same time, (+)-**7** was alkylated with benzyl bromide, which also afforded (+)-**9** (81%), exhibiting the



a) PMB-NH_2, $MgSO_4$, Et_2O, 0 °C. b) vinylMgCl/THF, Et_2O, 0 °C to rt. c) $H_2C{=}CH(CH_2)_2Br$, NaI, *n*-Bu_4NI, K_2CO_3, DMF, 70 °C. d) $ClCO_2Me$, Na_2CO_3, C_6H_6, reflux.

Scheme 3. Synthesis of carbamate (−)-**11**

same optical rotation and confirming that no racemization had occurred during the addition of vinylmagnesium chloride to imine **6** (Scheme 4).

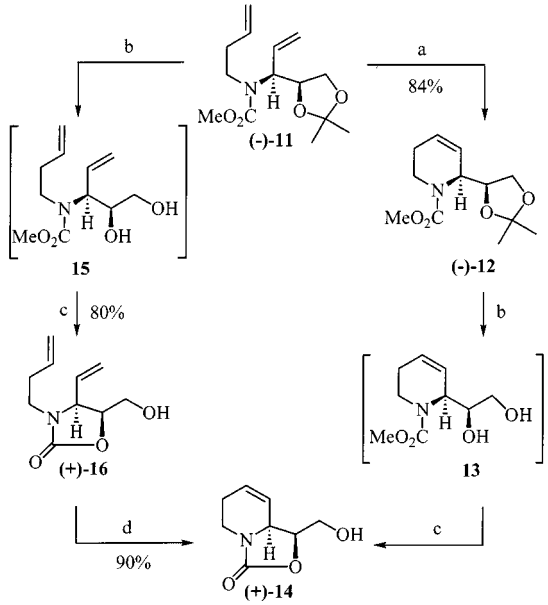


a) vinylMgCl, THF, Et_2O.[20] b) PMBBr, K_2CO_3, *n*-Bu_4NI, CH_3CN. c) BnBr, K_2CO_3, *n*-Bu_4NI, CH_3CN.

Scheme 4. Synthesis of allylic amine (+)-**9** from (+)-**7** and (+)-**8**

The alkylation of (+)-**7** was carried out with 4-bromobut-1-ene in the presence of potassium carbonate and sodium iodide in DMF at 70−100 °C. In most initial attempts, low and limited degrees of conversion into the desired tertiary amine (+)-**10** were observed (30%). Slightly improved results were obtained when one equivalent of the soluble iodide source *n*Bu_4NI was used, but the isolated yield of (+)-**10** remained quite low (38%), even though unchanged (+)-**7** (50%) could easily be recovered and recycled. However, we discovered that the concentration of the reaction mixture had a significant effect on the yield: performing the alkylation at a concentration of 2.7 mol·L^{-1} in **7** instead of 0.3 mol·L^{-1} raised the isolated yield of (+)-**10** to 74%, despite the completely heterogeneous character of the reaction mixture. The tertiary amine (+)-**10** was then debenzylated with methyl chloroformate[22] to afford the corresponding carbamate (−)-**11** (91%). It is worth emphasizing the high regioselectivity observed in this reaction, even though the amine (+)-**10** is also allylic (Scheme 3).

The next steps included the formation of the tetrahydropyridine ring, and functional group manipulation of the isopropylidene ketal and carbamate in order to elaborate the urethane five-membered ring of (−)-4a,5-dihydrostreptazolin. Treatment of the carbamate (−)-**11** with a catalytic amount of Grubbs' catalyst[23] in CH_2Cl_2 efficiently afforded the corresponding tetrahydropyridine (−)-**12** (84%). The acetonide was easily hydrolyzed with 80% aqueous AcOH, and subsequent treatment of the crude intermediate diol **13** with methanolic potassium hydroxide afforded the alcohol (+)-**14**; however, the latter was contaminated with an unidentified impurity that could not be efficiently separated. No attempts were made to optimize this reaction, since it was found advantageous to reverse the order of these two steps, with the ring-closing metathesis occurring preferentially later in the synthesis. Thus, hydrolysis of the acetonide of (−)-**11** afforded a crude diol **15**, which was quantitatively cyclized to urethane (+)-**16** (80%, two steps), by treatment with a methanolic potassium hydroxide solution. At this stage, the ring-closing metathesis proceeded efficiently and treatment of (+)-**16** with a catalytic amount of Grubbs' catalyst (3 mol %)[23] afforded (+)-**14** (90%), highlighting the remarkable functional group tolerance of this reaction, which does not require the protection of the alcohol function (Scheme 5).

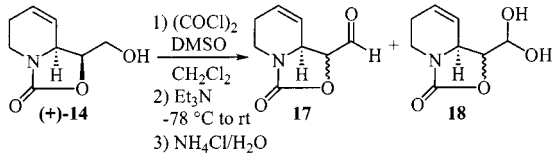


a) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2, reflux. b) 80% aqueous AcOH, 80 °C. c) 10% KOH, CH_3OH, rt. d) $Cl_2(PCy_3)_2Ru{=}CHPh$ (3 mol%), C_6H_6, 60 °C.

Scheme 5. Synthesis of tetrahydropyridine (+)-**14**

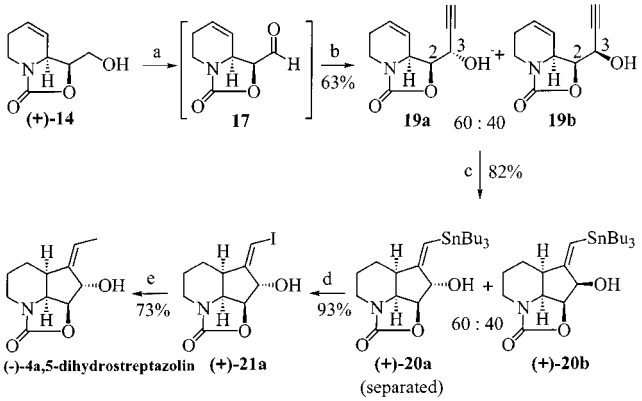
The oxidation of (+)-**14** into the corresponding aldehyde **17** turned out to be problematic. Use of buffered PCC[24] gave a complex mixture of products, whereas Dess−Martin,[25] Parikh−Doering,[26] and Swern[27] oxidations, followed by aqueous workup, afforded mixtures of products in which the desired aldehyde **17** and variable

quantities of its inseparable, highly water-soluble hydrate **18** could be identified. Moreover, in the last case epimerization at C-2a seemed to occur to a significant extent (ca. 15%) (Scheme 6). Thus, aldehyde **17** could not be isolated by an aqueous workup and its low solubility in nonpolar solvents precluded their use to precipitate the ammonium salts after completion of the Swern oxidation. Moreover, the temperature had to be carefully controlled in order to avoid the epimerization of the aldehyde, probably by triethylamine.



Scheme 6. Oxidation of alcohol (+)-**14**

Therefore, upon completion of the Swern oxidation, a large excess of ethynylmagnesium bromide was added directly to the reaction mixture. Under these conditions, no efficient diastereocontrol could occur and a mixture of the diastereomeric propargyl alcohols **19a** and **19b** was obtained (63%, 60:40 ratio). They were not separated at this stage but treated directly with tributyltin hydride in the presence of AIBN in refluxing benzene. This radical-mediated enyne cyclization afforded a 60:40 mixture of two diastereomeric vinylstannanes (+)-**20a** and (+)-**20b**, which were readily separated by flash chromatography (Scheme 7). In these compounds, the relative configuration was unambiguously assigned by differential NOE. Both vinylstannanes exhibit a *cis*-fused ring junction and a *Z* olefinic configuration, as suggested by the reciprocal intensity enhancement caused by irradiation of the signals corresponding to H-4a and H-7b, as well as H-8 and one proton (H-5) of the tetrahydropyridine ring. Moreover, no NOE was observed between H-2a and H-3 in (+)-**20a**, in contrast to (+)-**20b**, indicating that the major diastereomer (+)-**20a** has the required configuration at C-2a and C-3 for the synthesis of (−)-4a,5-dihydrostreptazolin. (Figure 2).



a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C then Et_3N, -78 °C to -40 °C. b) ethynylMgBr, THF, -78 °C to rt. c) *n*-Bu_3SnH, cat. AIBN, C_6H_6, reflux. d) I_2, CH_2Cl_2, 0 °C. e) CH_3ZnBr (from CH_3Li+$ZnBr_2$), cat. $Pd(PPh_3)_4$, THF/DMF, 60 °C.

Scheme 7. Total synthesis of (−)-4a,5-dihydrostreptazolin

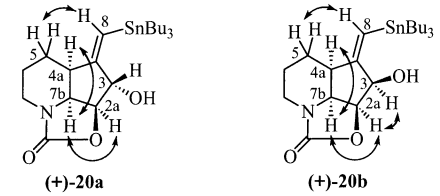


Figure 2. Differential NOE observed for diastereomers (+)-**20a** and (+)-**20b**

Finally, completion of the synthesis required the exchange of the tributylstannyl group for a methyl one. To this end, (+)-**20a** was first iododestannylated to afford (+)-**21a** (93%). The latter was insoluble in most organic solvents and so the organotin residues could easily be removed by extensive washing with a pentane/ether mixture. For introduction of the methyl group, we first investigated the use of Me_2CuLi in ether,[28] but the result was not satisfactory since inseparable mixtures of reduced product and (−)-4a,5-dihydrostreptazolin were formed even in the presence of methyl iodide. Fortunately, (+)-**21a** could be coupled with MeZnBr in THF/DMF[29] to give (−)-4a,5-dihydrostreptazolin (73%) {m.p. 161 °C, $[\alpha]_D^{20} = -43$ (c = 0.67, $CHCl_3$)} (Scheme 7). Its structure was unambiguously confirmed by an X-ray crystallographic analysis (Figure 3), although the previously reported optical rotation and melting point for this compound were lower {m.p. 154−155 °C, $[\alpha]_D^{23} = -24.3$ (c = 0.54, $CHCl_3$)}.[11]

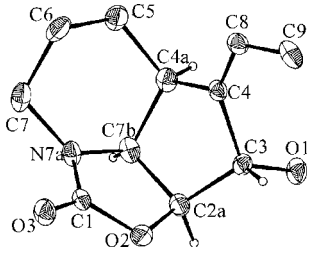


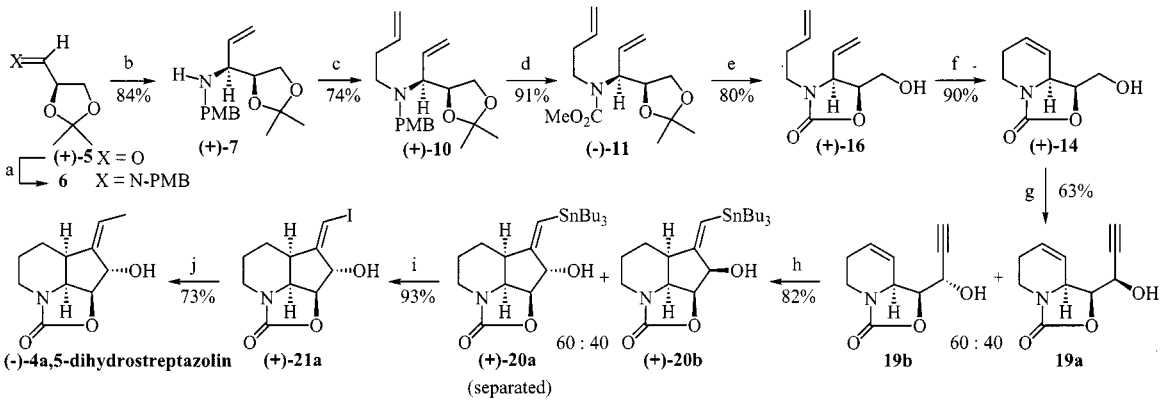
Figure 3. ORTEP diagram for (−)-4a,5-dihydrostreptazolin

Thus (−)-4a,5-dihydrostreptazolin has been synthesized in nine steps from D-glyceraldehyde acetonide, in 9% overall yield (Scheme 8).

The epimeric vinylstannane (+)-**20b** was similarly converted into the vinyl iodide (+)-**21b** (88%) and the latter was also coupled with methylzinc bromide to afford (+)-4a,5-dihydro-3-epistreptazolin **22** (50%). Finally, palladium-catalyzed cross-coupling of (+)-**21a** with PhZnBr and vinylZnBr afforded compounds (−)-**23** (58%) and (−)-**24** (62%) respectively, illustrating the synthetic interest of intermediate (+)-**21a** for the synthesis of structures related to (−)-4a,5-dihydrostreptazolin (Scheme 9).

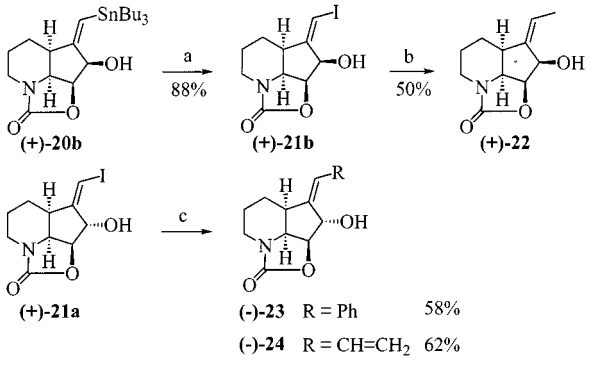
Conclusion

We report a short and efficient synthesis of (−)-4a,5-dihydrostreptazolin, in nine steps from D-glyceraldehyde ace-



a) PMB-NH_2, $MgSO_4$, Et_2O, 0 °C. b) vinylMgCl/THF, Et_2O, 0 °C to rt. c) $H_2C{=}CH(CH_2)_2Br$, NaI, *n*-Bu_4NI, K_2CO_3, DMF, 70 °C. d) $ClCO_2Me$, Na_2CO_3, C_6H_6, reflux . e) 80% aq.AcOH, 80 °C then10% KOH, MeOH, rt. f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (3 mol%), C_6H_6, 60 °C. g) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N, -78 °C to -40 °C, then ethynylmagnesium bromide/THF, -78 °C to rt. h) *n*-Bu_3SnH, cat. AIBN, C_6H_6, reflux. i) I_2, CH_2Cl_2, 0 °C. j) CH_3ZnBr, cat. $Pd(PPh_3)_4$, THF, DMF, 60 °C.

Scheme 8. Total synthesis of (−)-4a,5-dihydrostreptazolin



a) I_2, CH_2Cl_2, rt. b) CH_3ZnBr (from CH_3Li+$ZnBr_2$), cat. $Pd(PPh_3)_4$, THF/DMF, 60 °C. c) PhZnBr (from PhLi+$ZnBr_2$) or vinylZnBr (from vinylMgCl+$ZnBr_2$), cat. $Pd(PPh_3)_4$, THF/DMF, 60 °C.

Scheme 9. Synthesis of structural analogues of 4a,5-dihydrostreptazolin

tonide, and in 9% overall yield. The stereoselective construction of the tetrahydropyridine ring was performed using a vinylic Grignard reagent addition to an imine derived from D-glyceraldehyde acetonide and a ring-closing metathesis reaction. Elaboration of the five-membered ring was carried out by a highly stereoselective radical-mediated enyne cyclization. Furthermore, this strategy permits the formation of derivatives of dihydrostreptazolin by cross-coupling reactions with various organometallic reagents. The biological properties of these compounds are currently being evaluated.

Experimental Section

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. − THF and ether were distilled from sodium/benzophenone ketyl immediately before use. − Dichloromethane, DMF, DMSO, toluene, benzene, acetonitrile, and triethylamine were distilled from calcium hydride. − Zinc bromide was melted and cooled under argon. − Moisture-sensitive reactions were conducted in oven-dried glassware under argon. − Analytical thin layer chromatography was performed on Merck precoated silica gel (60 F_{254}). − Flash chromatography was performed with Merck Kieselgel 60 (230−400 mesh). − Melting points were measured on a Kofler apparatus. − IR: Perkin−Elmer 298 spectrometer. − Optical rotations: Perkin−Elmer 241MC polarimeter. − Elemental analyses: Service Régional de Microanalyses de l'Université P. et M. Curie (Paris VI). − HRMS: Laboratoire de Spectrochimie de l'Ecole Normale Supérieure Ulm. − NMR: Bruker AC 300 spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). Chemical shifts (δ) are expressed in ppm relative to TMS. − MS: Mass spectra were obtained by GC/MS with electron impact ionization using a 5971 Hewlett Packard instrument at 70 eV.

***N*-[(1*S*)-1-{(4*S*,5*S*)-5-[(*tert*-Butyldiphenylsiloxy)methyl]-2,2-dimethyl-1,3-(dioxolan-4-yl)prop-2-enyl}]-4-methoxybenzylamine [(−)-4]:** A solution of DMSO (2.60 mL, 36.6 mmol, 3.7 equiv.) in CH_2Cl_2 (6 mL) was added dropwise at −78 °C to a solution of oxalyl dichloride (1.46 mL, 16.7 mmol, 1.7 equiv.) in CH_2Cl_2 (40 mL). After 25 min, a solution of (−)-**1** (4.0 g, 10 mmol) in CH_2Cl_2 (13 mL) was added dropwise at −78 °C. After a further 15 min, Et_3N (7.0 mL, 50 mmol, 5.0 equiv.) was added over 5 min, and the reaction was then allowed to warm slowly to room temp. After 1 h, water (20 mL) was added to the reaction mixture, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude aldehyde **2** (3.9 g) was dissolved in ether (50 mL). 4-Methoxybenzylamine (1.15 mL, 8.80 mmol, 0.90 equiv.) and anhydrous $MgSO_4$ (3 g) were then added and, after 3 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude imine **3** (4.9 g) was dissolved in ether (35 mL) and added dropwise to a solution of vinylmagnesium bromide (22 mL, 1 M in THF, 22 mmol, 2.5 equiv.) at 0 °C. After 18 h at room temp., the reaction mixture was quenched with a mixture of 32% aqueous NH_4OH/saturated aqueous NH_4Cl (1:2), and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2CO_3, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 90:10) on silica gel previously impregnated with the eluent containing 1% of 32% aqueous NH_4OH solution. Compound (−)-**4** (1.9 g, 35%) was obtained as an orange oil. − $[\alpha]_D^{20} = -13$ (*c* =

1.05, $CHCl_3$). − IR (neat): ṽ= 3330, 1610, 1585, 1510, 1245, 1170, 1110, 1000 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.97 (s, 9 H), 1.32 (s, 6 H), 1.62 (br. s, 1 H), 3.24 (dd, *J* = 8.5, 4.1 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 3.58−3.81 (3 H), 3.71 (s, 3 H), 4.04 (m, 1 H), 4.14 (dd, *J* = 8.1, 4.1 Hz, 1 H), 5.17 (dd, *J* = 17.3, 1.8 Hz, 1 H), 5.31 (dd, *J* = 10.3, 1.8 Hz, 1 H), 5.74 (ddd, *J* = 17.3, 10.3, 8.5 Hz, 1 H), 6.85 (m, 2 H), 7.23 (m, 2 H), 7.35−7.46 (6 H), 7.66−7.72 (4 H). − ^{13}C NMR ($CDCl_3$): δ = 19.2 (s), 26.8 (q), 27.1 (q), 50.2 (t), 55.2 (q), 61.7 (d), 64.7 (t), 78.4 (d), 81.4 (d), 108.8 (s), 113.7 (d), 118.6 (t), 127.6 (d), 129.3 (d), 129.7 (d), 132.5 (s), 133.2 (s), 135.6 (d), 136.3 (d), 158.5 (s). − MS (EI): *m*/*z* (%) = 545 (0.1) [M^+], 176 (33), 136 (13), 121 (100).

***N*-{(1*S*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]prop-2-enyl}-4-methoxybenzylamine [(+)-7]:** Anhydrous $MgSO_4$ (30 g) was added to a solution of D-glyceraldehyde acetonide (+)-**5** (19.8 g, 153 mmol) and 4-methoxybenzylamine (20.4 mL, 156 mmol, 1.02 equiv.) in ether (300 mL) at 0 °C. After 3 h at 0 °C, the reaction mixture was filtered and concentrated under reduced pressure to give 38.1 g (100%) of imine **6** as a slightly yellow liquid, which was used directly in the next step. A solution of **6** (36.6 g, 147 mmol) in ether (350 mL) was added dropwise at 0 °C to a solution of vinylmagnesium chloride (218 mL, 1.68 M in THF, 366 mmol, 2.5 equiv.). After stirring overnight at room temp., the reaction was quenched with a mixture of 32% aqueous NH_4OH/saturated aqueous NH_4Cl: 1:2, and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2CO_3, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt/NH_4OH, 90:10:0.1) to give 34.0 g (84%) of (+)-**7** as a yellow liquid. − $[\alpha]_D^{20}$ = +21 (*c* = 1.14, $CHCl_3$). − IR (neat): ṽ = 3320, 3060, 1640, 1610, 1785, 1510, 1240, 1170, 1140 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.35 (s, 3 H), 1.41 (s, 3 H), 1.65 (br. s, 1 H), 3.17 (dd, *J* = 8.1, 4.8 Hz, 1 H), 3.58 (d, *J* = 12.9 Hz, 1 H), 3.80 (s, 3 H), 3.81 (d, *J* = 12.9 Hz, 1 H), 3.89 (dd, *J* = 8.1, 7.0 Hz, 1 H), 4.00 (dd, *J* = 8.1, 6.6 Hz, 1 H), 4.13 (ddd, *J* = 7.0, 6.6, 4.8 Hz, 1 H), 5.22 (ddd, *J* = 17.3, 1.8, 0.7 Hz, 1 H), 5.30 (ddd, *J* = 10.3, 1.8, 0.7 Hz, 1 H), 5.68 (ddd, *J* = 17.3, 10.3, 8.1 Hz, 1 H), 6.86 (m, 2 H), 7.24 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.0 (q), 26.3 (q), 50.1 (t), 55.1 (q), 61.8 (d), 66.0 (t), 78.2 (d), 108.9 (s), 113.6 (d), 118.3 (t), 129.1 (d), 132.4 (s), 136.4 (d), 158.4 (s). − MS (EI): *m*/*z* (%) = 278 (0.05) [M^+], 176 (21), 121 (100). − $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.30, H 8.45, N 4.96.

***N*-Benzyl-*N*-{(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enyl}-4-methoxybenzylamine [(+)-9]**

Synthesis from (+)-8: Anhydrous K_2CO_3 (780 mg, 5.66 mmol, 2.0 equiv.), nBu_4NI (100 mg, 0.28 mmol, 0.1 equiv.), and *p*-methoxybenzyl bromide (630 mg, 3.11 mmol, 1.1 equiv.) were added successively to a solution of (+)-**8**[21] (700 mg, 2.83 mmol) in CH_3CN (6 mL). After 1 h at 40 °C and overnight at room temp., the reaction mixture was diluted with ether, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 95:5 to 90:10) to give 0.68 g (65%) of (+)-**9** as a colorless oil. − $[\alpha]_D^{20}$ = +12.5 (*c* = 2.02, $CHCl_3$).

Synthesis from (+)-7: Anhydrous K_2CO_3 (500 mg, 3.62 mmol, 2.0 equiv.), nBu_4NI (66 mg, 0.18 mmol, 0.1 equiv.), and benzyl bromide (0.24 mL, 1.98 mmol, 1.1 equiv.) were added successively to a solution of (+)-**7** (500 mg, 1.81 mmol) in CH_3CN (5 mL). After 2 h at 35−40 °C and overnight at room temp., the reaction mixture was diluted with ether, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (cyclohexane/AcOEt, 95:5 to 90:10) to give 0.54 g (81%) of (+)-**9** as a colorless oil. − $[\alpha]_D^{20}$ = +12.9 (*c* = 1.99, $CHCl_3$). − IR (neat): ṽ = 3060, 1610, 1580, 1510, 1170, 1060 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.23 (s, 3 H), 1.30 (s, 3 H), 2.97 (dd, *J* = 9.0, 7.7 Hz, 1 H), 3.28 (d, *J* = 13.2 Hz, 1 H), 3.32 (d, *J* = 13.8 Hz, 1 H), 3.59 (dd, *J* = 8.3, 7.4 Hz, 1 H), 3.76 (s, 3 H), 3.76 (d, *J* = 13.2 Hz, 1 H), 3.84 (d, *J* = 13.8 Hz, 1 H), 4.11 (dd, *J* = 8.3, 6.3 Hz, 1 H), 4.30 (ddd, *J* = 7.7, 7.4, 6.3 Hz, 1 H), 5.17 (ddd, *J* = 17.2, 2.2, 0.7 Hz, 1 H), 5.46 (ddd, *J* = 10.3, 2.2, 0.4 Hz, 1 H), 5.95 (ddd, *J* = 17.2, 10.3, 9.0 Hz, 1 H), 6.84 (m, 2 H), 7.20−7.26 (3 H), 7.29−7.31 (4 H). − ^{13}C NMR ($CDCl_3$): δ = 25.6 (q), 26.4 (q), 54.0 (t), 54.5 (t), 55.1 (q), 63.9 (d), 68.5 (t), 76.8 (d), 109.2 (s), 113.6 (d), 120.6 (t), 126.9 (d), 128.2 (d), 128.7 (d), 129.8 (d), 131.6 (s), 132.2 (d), 139.8 (s), 158.6 (s). − MS (EI): *m*/*z* (%) = 367 (0.5) [M^+], 266 (47), 121 (100), 91 (11).

***N*-(But-3-enyl)-*N*-{(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enyl}-4-methoxybenzylamine [(+)-10]:** Anhydrous K_2CO_3 (11.2 g, 81.2 mmol, 3.0 equiv.), NaI (8.10 g, 54.0 mmol, 2.0 equiv.), and nBu_4NI (9.97 g, 27.1 mmol, 1.0 equiv.) were added successively to a solution of (+)-**7** (7.50 g, 27.1 mmol) in DMF (10 mL). After 15 h at 70 °C, the reaction mixture was diluted with Et_2O and filtered through Celite. The insoluble salts were thoroughly washed with ether and the filtrate was washed with water and brine, and dried over Na_2CO_3. After filtration and concentration under reduced pressure, the crude material was purified by flash chromatography (petroleum ether/AcOEt, 95:5 to 90:10) to give 6.6 g (74%) of (+)-**10** as a yellow liquid. − $[\alpha]_D^{20}$ = + 60 (*c* = 1.10, $CHCl_3$). − IR (neat): ṽ = 3070, 1640, 1610, 1585, 1510, 1250, 1060, 1035 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.32 (s, 3 H), 1.35 (s, 3 H), 2.17−2.25 (2 H), 2.45 (ddd, *J* = 12.9, 7.0, 5.4 Hz, 1 H), 2.67 (dt, *J* = 12.9, 8.1 Hz, 1 H), 2.97 (dd, *J* = 8.8, 8.5 Hz, 1 H), 3.31 (d, *J* = 13.6 Hz, 1 H), 3.72 (dd, *J* = 8.5, 6.8 Hz, 1 H), 3.77 (d, *J* = 13.6 Hz, 1 H), 3.81 (s, 3 H), 4.10 (dd, *J* = 8.5, 6.2 Hz, 1 H), 4.21 (m, 1 H), 4.98−5.09 (2 H), 5.19 (m, 1 H), 5.42 (dd, *J* = 10.3, 2.2 Hz, 1 H), 5.76 (ddt, *J* = 16.9, 10.1, 6.8 Hz, 1 H), 5.89 (ddd, *J* = 16.9, 10.3, 8.8 Hz, 1 H), 6.86 (m, 2 H), 7.21 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.6 (q), 26.6 (q), 33.1 (t), 50.0 (t), 54.3 (t), 55.1 (q), 65.1 (d), 68.6 (t), 76.5 (d), 109.2 (s), 113.5 (d), 115.5 (t), 120.0 (t), 129.7 (d), 131.8 (s), 132.6 (d), 136.8 (d), 158.5 (s). − MS (EI): *m*/*z* (%) = 331 (0.02) [M^+], 316 (1.5) [M − CH_3^+], 231 (8), 230 (44), 122 (9), 121 (100). − $C_{20}H_{29}NO_3$ (331.45): calcd. C 72.47, H 8.81, N 4.22; found C 72.52, H 8.87, N 4.13.

Methyl *N*-(But-3-enyl)-*N*-{(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enyl}carbamate [(−)-11]: Anhydrous Na_2CO_3 (20.0 g, 189 mmol, 7.0 equiv.) and $ClCO_2CH_3$ (14.5 mL, 189 mmol, 7.0 equiv.) were added to a solution of (+)-**10** (8.90 g, 26.9 mmol) in benzene (160 mL). After 15 h at 75 °C, additional $ClCO_2CH_3$ (5.0 mL, 65 mmol, 2.4 equiv.) was added and the reaction mixture was refluxed. After 2 h, the reaction mixture was cooled to room temp., filtered, and concentrated under reduced pressure, and the crude material was purified by flash chromatography (cyclohexane/AcOEt, 95:5) to give 6.6 g (91%) of (−)-**11** as a yellow liquid. − $[\alpha]_D^{20}$ = −15 (*c* = 2.08, $CHCl_3$). − IR (neat): ṽ = 3070, 1710, 1640, 1150, 1060 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.35 (s, 3 H), 1.43 (s, 3 H), 2.21−2.40 (2 H), 3.18−3.35 (2 H), 3.71 (s, 3 H), 3.75 (dd, *J* = 8.5, 6.2 Hz, 1 H), 4.04 (dd, *J* = 8.5, 6.2 Hz, 1 H), 4.27−4.45 (2 H), 5.01−5.10 (2 H), 5.20−5.33 (2 H), 5.75 (ddt, *J* = 16.9, 10.3, 7.0 Hz, 1 H), 6.01 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.2 (q), 26.6 (q), 34.0 (t), 45.3 (t), 52.5 (q), 61.4 (d), 67.1 (t), 76.5 (d), 109.8 (s), 116.4 (t), 119.0 (t), 132.9 (d), 135.1 (d), 156.7 (s). − MS (EI): *m*/*z* (%) = 254 (16) [M − CH_3^+], 228 (12), 170 (14), 169 (14), 168 (100), 140 (11), 128 (12), 127 (23), 101 (71), 88 (20), 81 (14), 55

(11). − $C_{14}H_{23}NO_4$ (269.34): calcd. C 62.43, H 8.61, N 5.20; found C 62.33, H 8.77, N 5.14.

Methyl 6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate [(−)-12]: A solution of $Cl_2(PCy_3)_2Ru{=}CHPh$ (93 mg, 0.11 mmol, 0.05 equiv.) in CH_2Cl_2 (5 mL) was added in four portions at 20 min intervals to a refluxing degassed solution of (−)-**11** (610 mg, 2.27 mmol) in CH_2Cl_2 (20 mL). After 18 h at reflux, the reaction mixture was cooled to room temp., exposed to air and, after 2 h, concentrated under reduced pressure. The crude material was purified by chromatography (cyclohexane/AcOEt, 80:20) to give 450 mg (84%) of (−)-**12**, as a slightly green oil. − $[\alpha]_D^{20}$ = −266 (*c* = 1.50, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3030, 1700, 1655, 1255, 1200, 1150, 1105, 1055 cm^{-1}. − ^1H NMR ($CDCl_3$) *All signals are broad, due to the presence of rotamers*: δ = 1.34 (s, 3 H), 1.44 (s, 3 H), 1.97 (m, 1 H), 2.20 (m, 1 H), 3.01 (m, 1 H), 3.72 (s, 3 H), 4.60−4.85 (5 H), 5.82 (m, 1 H), 5.97 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 24.3 and 24.7 (t, 2 rotamers), 25.3 (q), 26.6 and 26.8 (q, 2 rotamers), 38.1 and 38.7 (t, 2 rotamers), 52.6 (q), 54.2 (d), 67.2 (t), 77.9 (d), 109.6 (s), 125.1 (d), 126.8 and 127.2 (d, 2 rotamers), 156.0 (s). − MS (EI): *m*/*z* (%) = 241 (2) [M^+], 140 (100), 101 (92), 73 (11).

(4*S*,5*S*)-4-(Hydroxymethyl)-3-oxa-1-azabicyclo[4.3.0]non-6-en-2-one [(+)-14]:

Synthesis from (−)-12: Compound (−)-**12** (509 mg, 2.11 mmol) was added to an 80% aqueous solution of acetic acid (40 mL). After 1 h at 80 °C, the reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was diluted with toluene and evaporated again. The crude material was dissolved in a 10% KOH solution in methanol (15 mL). After 3 h at room temp. the reaction mixture was concentrated under reduced pressure. The residue was neutralized at 0 °C by addition of a 3 M aqueous solution of hydrochloric acid and extracted several times with AcOEt. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/EtOH, 95:5) to give 300 mg of (+)-**14** as an oil, which was contaminated with an unidentified inseparable impurity [spectroscopic data of (+)-**14** are listed under the synthesis of this compound from (+)-**16**].

(4*S*,5*S*)-3-(But-3-enyl)-4-ethenyl-5-(hydroxymethyl)oxazolidin-2-one [(+)-16]: Compound (−)-**11** (3.50 g, 13.0 mmol) was added to an 80% aqueous solution of acetic acid (200 mL). After 4 h at 80 °C, the reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was diluted with toluene and evaporated again. The crude material was dissolved in a 10% solution of KOH in methanol (50 mL). After 2 h at room temp., the reaction mixture was concentrated under reduced pressure. The residue was neutralized at 0 °C with a 3 M aqueous solution of hydrochloric acid, and extracted with AcOEt. The combined extracts were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude material was purified by flash chromatography (CH_2Cl_2/AcOEt, 75:25) to give 2.04 g (80%) of (+)-**16** as a yellow oil. − $[\alpha]_D^{20}$ = +26 (*c* = 1.00, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3400, 3070, 1740, 1640, 1420, 1220, 835, 760 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.21−2.35 (2 H), 2.53 (t, *J* = 6.3 Hz, 1 H, OH), 3.03 (ddd, *J* = 14.0, 7.4, 5.9 Hz, 1 H), 3.51 (dt, *J* = 14.0, 7.4 Hz, 1 H), 3.74−3.78 (2 H), 4.34 (dd, *J* = 9.2, 8.8 Hz, 1 H), 4.61 (dt, *J* = 8.8, 5.0 Hz, 1 H), 5.04−5.15 (2 H), 5.38−5.45 (2 H), 5.69−5.92 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 31.7 (t), 41.2 (t), 61.0 (d), 61.3 (t), 76.7 (d), 117.3 (t), 122.4 (t), 131.8 (d), 134.7 (d), 157.3 (s). − MS (EI): *m*/*z* (%) = 197 (0.3) [M^+], 156 (100) [M − $C_3H_5^+$], 82 (11), 68 (67), 67 (22), 55 (35), 53 (10). − $C_{10}H_{15}NO_3$ (197.24): calcd. C 60.90, H 7.66, N 7.10; found C 60.73, H 7.88, N 7.04.

(4*S*,5*S*)-4-(Hydroxymethyl)-3-oxa-1-azabicyclo[4.3.0]non-6-en-2-one [(+)-14]

Synthesis from (+)-16: A degassed solution of (+)-**16** (1.20 g, 6.09 mmol) in benzene (150 mL) was warmed to 55 °C and 1 mL of a solution of $Cl_2(PCy_3)_2Ru{=}CHPh$ [150 mg, 0.18 mmol, 0.03 equiv., in benzene (7 mL)] was added every 20 min. After 1 h at 60 °C and overnight at room temp., the reaction mixture was exposed to air. After 2 h, the resulting mixture was concentrated under reduced pressure and the crude material was purified by chromatography (CH_2Cl_2/AcOEt, 80:20 to 0:100) to give 930 mg (90%) of (+)-**14** as a gray solid. − m.p. 67−70 °C. − $[\alpha]_D^{20}$ = +153 (*c* = 1.67, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3400, 3030, 1740, 1645, 1445, 1430, 1230, 1055, 1035 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.05 (m, 1 H), 2.22 (m, 1 H, OH), 2.36 (m, 1 H), 3.04 (ddd, *J* = 13.4, 11.4, 4.6 Hz, 1 H), 3.72−3.75 (2 H), 3.94 (dd, *J* = 13.6, 6.8 Hz, 1 H), 4.52 (m, 1 H), 4.70 (dt, *J* = 8.8, 5.5 Hz, 1 H), 5.70 (m, 1 H), 6.03 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.3 (t), 38.0 (t), 54.2 (d), 61.1 (t), 77.1 (d), 122.0 (d), 128.7 (d), 157.0 (s). − MS (EI): *m*/*z* (%) = 169 (48) [M^+], 139 (18), 138 (100) [M − CH_2OH^+], 82 (16), 81 (48), 80 (26), 67 (20), 56 (16), 54 (15).

(3*S*,4*S*)-4-[(1*S*)-1-Hydroxyprop-2-ynyl]-3-oxa-1-azabicyclo-[4.3.0]non-6-en-2-one (19a) and (3*S*,4*S*)-4-[(1*R*)-1-Hydroxyprop-2-ynyl]-3-oxa-1-azabicyclo[4.3.0]non-6-en-2-one (19b): DMSO (3.10 mL, 43.4 mmol, 3.5 equiv.) was added dropwise at −78 °C to a solution of oxalyl dichloride (1.81 mL, 21.1 mmol, 1.7 equiv.) in CH_2Cl_2 (40 mL). After 10 min, a solution of (+)-**14** (2.10 g, 12.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −78 °C. After 20 min, Et_3N (5.20 mL, 37.3 mmol, 3.0 equiv.) was added and the reaction was gradually warmed to −40 °C. After 1 h, ethynylmagnesium bromide (200 mL, 0.5 M in THF, 100 mmol, 8.1 equiv.) was introduced slowly at −78 °C. The reaction mixture was warmed to 0 °C, poured into a saturated aqueous solution of NH_4Cl, and extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure, and the crude material was purified by flash chromatography (petroleum ether/AcOEt, 40:60 to 0:100) to give 1.50 g (63%) of a 60:40 diastereomeric mixture of **19a** and **19b** as a white solid. − IR (KBr): $\tilde{\nu}$ = 3396, 3237, 2112, 1720, 1445, 1120, 1056 cm^{-1}.

Compound 19a: ^1H NMR (CD_3OD): δ = 2.24 (m, 1 H), 2.52 (m, 1 H), 3.22 (d, *J* = 2.6 Hz, 1 H), 3.27 (m, 1 H), 4.02 (dd, *J* = 13.6, 6.6 Hz, 1 H), 4.60 (dd, *J* = 6.2, 2.2 Hz, 1 H), 4.78−4.86 (2 H), 6.09−6.25 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 23.1 (t), 38.5 (t), 54.5 (d), 61.6 (d), 75.9 (d), 78.6 (d), 79.8 (s), 121.9 (d), 129.7 (d), 156.6 (s). − MS (EI): *m*/*z* (%) = 164 (4), 139 (13), 138 (100) [M − $C_3H_3O^+$], 132 (15), 94 (21), 93 (18), 81 (14), 80 (19), 67 (17), 56 (15), 55 (14), 53 (12).

Compound 19b: ^1H NMR (CD_3OD): δ = 2.24 (m, 1 H), 2.52 (m, 1 H), 3.12 (d, *J* = 2.2 Hz, 1 H), 3.27 (m, 1 H), 4.03 (dd, *J* = 13.2, 6.6 Hz, 1 H), 4.57 (dd, *J* = 5.2, 2.2 Hz, 1 H), 4.78−4.86 (2 H), 6.09−6.25 (2 H). − ^{13}C NMR ($CDCl_3$): δ = 23.4 (t), 38.0 (t), 54.1 (d), 61.9 (d), 75.9 (d), 78.3 (d), 80.2 (s), 121.9 (d), 129.2 (d), 156.4 (s). − MS (EI): *m*/*z* (%) = 149 (7) [M − CO_2^+], 139 (12), 138 (100) [M − $C_3H_3O^+$], 132 (15), 94 (25), 93 (17), 81 (18), 80 (21), 67 (20), 56 (17), 53 (18). − $C_{10}H_{11}NO_3$ (193.20): calcd. C 62.17, H 5.74, N 7.25; found C 62.10, H 5.75, N 7.12.

Radical-Mediated Cyclisation of 19a and 19b: Bu_3SnH (910 μL, 3.37 mmol, 1.3 equiv.) was added to a solution of **19a** and **19b** (500 mg, 60:40 diastereomeric mixture, 2.59 mmol) and AIBN (17 mg, 0.10 mmol, 0.04 equiv.) in refluxing benzene (130 mL). After 1 h and 2 h, the same quantities of AIBN and Bu_3SnH were added again to the reaction mixture. After a further 3 h reflux, the

reaction mixture was concentrated under reduced pressure and the crude material purified by filtration through silica gel (cyclohexane/CH_2Cl_2, 20:80, then CH_2Cl_2, then CH_2Cl_2/AcOEt, 95:5) to give 380 mg (30%) of (+)-**20b** and 640 mg (52%) of (+)-**20a** as white solids.

(5*S*,6*Z*,7*S*,8*S*,11*S*)-6-(Tri-*n*-butylstannylmethylidene)-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(+)-20a]: − m.p. 71−72 °C. − $[\alpha]_D^{20}$ = +9 (*c* = 1.25, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3336, 2853, 1722, 1456, 1425, 1245, 1035 cm^{-1}. − ^{1}H NMR (C_6D_6): δ = 0.82 (m, 1 H), 0.98−1.09 (17 H), 1.36−1.46 (7 H), 1.58−1.67 (6 H), 1.90 (m, 1 H, OH), 2.21 (ddd, *J* = 15.1, 12.1, 2.9 Hz, 1 H), 2.61 (m, 1 H), 3.52 (m, 1 H), 3.75 (m, 1 H), 4.23 (br. d, *J* = 2.6 Hz, 1 H), 4.36 (d, *J* = 7.4 Hz, 1 H), 6.00 (d, *J* = 2.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 10.6 (t), 13.6 (q), 18.9 (t), 21.1 (t), 27.2 (t), 28.9 (t), 40.2 (d), 40.8 (t), 59.1 (d), 79.6 (d), 81.2 (d), 129.1 (d), 155.9 (s), 156.5 (s). − $C_{22}H_{39}NO_3Sn$ (484.27): calcd. C 54.57, H 8.12, N 2.89; found C 54.90, H 8.13, N 2.72.

(5*S*,6*Z*,7*R*,8*S*,11*S*)-6-(Tri-*n*-butylstannylmethylidene)-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(+)-20b]: − m.p. 45−46 °C. − $[\alpha]_D^{20}$ = +84 (*c* = 1.32, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3410, 2363, 1724, 1637, 1458, 1156, 1068, 1012 cm^{-1}. − ^{1}H NMR (C_6D_6): δ = 0.78 (m, 1 H), 0.98−1.14 (15 H), 1.38−1.50 (7 H), 1.64−1.81 (9 H), 2.17 (m, 1 H), 2.97 (d, *J* = 9.6 Hz, 1 H, OH), 3.21 (dd, *J* = 7.0, 5.5 Hz, 1 H), 3.65 (br. dd, *J* = 13.6, 4.4 Hz, 1 H), 4.01 (m, 1 H), 4.16 (dd, *J* = 7.0, 6.6 Hz, 1 H), 5.92 (apparent t, *J* = 2.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 11.6 (t), 13.7 (q), 19.1 (t), 20.8 (t), 27.3 (t), 29.2 (t), 38.5 (d), 41.2 (t), 57.2 (d), 73.8 (d), 74.8 (d), 123.8 (d), 153.2 (s), 155.7 (s). − $C_{22}H_{39}NO_3Sn$ (484.27): calcd. C 54.57, H 8.12, N 2.89; found C 54.93, H 8.19, N 2.76.

(5*S*,6*Z*,7*S*,8*S*,11*S*)-7-Hydroxy-6-iodomethylidene-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(+)-21a]: Iodine (580 mg, 2.29 mmol, 3.0 equiv.) was added to a solution of (+)-**20a** (370 mg, 0.76 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 1 h at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (4 mL) and extracted several times with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a solid material, which was washed twice with pentane/ether (2:1) and filtered. Analytically pure (+)-**21a** (230 mg, 93%) was obtained as a white solid. − m.p. 200−201 °C. − $[\alpha]_D^{20}$ = +64 (*c* = 0.70, DMSO). − IR (KBr): $\tilde{\nu}$ = 3318, 3062, 1718, 1235, 1078, 1029 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.16−1.37 (2 H), 1.77 (m, 1 H), 2.12 (m, 1 H), 2.77 (m, 1 H), 2.89 (m, 1 H), 3.52 (m, 1 H), 4.30 (d, *J* = 4.4 Hz, 1 H), 4.35 (m, 1 H), 4.61 (d, *J* = 7.4 Hz, 1 H), 5.70 (d, *J* = 4.4 Hz, 1 H, OH), 6.49 (d, *J* = 2.2 Hz, 1 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 18.7 (t), 20.0 (t), 40.1 (t), 40.2 (d), 58.7 (d), 78.5 (d), 79.9 (d), 81.2 (d), 151.2 (s), 155.0 (s).

(−)-4a, 5-Dihydrostreptazoline: Methyllithium (12.2 mL, 1.6 M in ether, 19.6 mmol, 7.0 equiv.) was added at 0 °C to a solution of anhydrous $ZnBr_2$ (5.0 g, 22 mmol, 8.0 equiv.) in THF (25 mL). After 20 min at room temp., a solution of (+)-**21a** (900 mg, 2.80 mmol) in DMF (15 mL) was added dropwise. Ten min later, $Pd(PPh_3)_4$ (100 mg, 0.08 mmol, 0.03 equiv.) was added and the reaction mixture was heated at 60 °C. After 2 h, the reaction mixture was cooled to 0 °C, poured into a saturated aqueous solution of NH_4Cl, and extracted with AcOEt. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (AcOEt). A slightly yellow, impure solid (550 mg) was obtained and recrystallized from benzene to give 430 mg (73%) of (−)-4a,5-dihydrostreptazolin as colorless crystals. − m.p. 161 °C. − $[\alpha]_D^{20}$ = −43 (*c* = 0.67, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3360, 1710, 1665, 1025, 1000 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.35−1.59 (2 H), 1.80 (dd, *J* = 6.9, 2.7 Hz, 3 H), 1.83 (m, 1 H), 2.12 (m, 1 H), 2.31 (d, *J* = 2.2 Hz, 1 H, OH), 2.78 (m, 1 H), 2.94 (m, 1 H), 3.79 (m, 1 H), 4.21 (dd, *J* = 7.0, 5.5 Hz, 1 H), 4.72 (d, *J* = 7.0 Hz, 1 H), 4.74 (br. s, 1 H), 5.54 (qdd, *J* = 6.9, 2.7, 1.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 14.2 (q), 18.5 (t), 20.6 (t), 38.5 (d), 40.6 (t), 59.0 (d), 74.7 (d), 81.2 (d), 123.8 (d), 138.9 (s), 156.0 (s). − MS (EI): *m*/*z* (%) = 209 (17) [M$^+$], 194 (43) [M$^+$ − CH_3], 165 (63), 164 (87), 150 (100), 148 (29), 136 (23), 122 (28), 95 (34), 79 (23), 67 (22), 55 (24). − $C_{11}H_{15}NO_3$ (209.24): calcd. C 63.14, H 7.23, N 6.69; found C 63.11, H 7.26, N 6.63.

(5*S*,6*Z*,7*R*,8*S*,11*S*)-7-Hydroxy-6-iodomethylidene-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(+)-21b]: Vinylstannane (+)-**20b** (1.20 g, 2.48 mmol) was converted into (+)-**21b** as described for the preparation of (+)-**21a** from (+)-**20a**, using iodine (1.90 g, 7.49 mmol, 3.0 equiv.) in CH_2Cl_2 (25 mL). The crude solid material was washed several times with pentane/ether (3:1), to give 700 mg (88%) of (+)-**21b** as a white solid. − m.p. 200−204 °C. − $[\alpha]_D^{20}$ = +111 (*c* = 1.20, DMSO). − IR (KBr): nu (tilde) = 3340, 1710, 1650, 1640, 1260, 1230, 1060, 1010 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.26−1.39 (2 H), 1.73 (m, 1 H), 2.04 (m, 1 H), 2.68 (m, 1 H), 2.82 (m, 1 H), 3.54 (m, 1 H), 4.41 (dd, *J* = 6.6, 6.3 Hz, 1 H), 4.48 (ddd, *J* = 6.6, 6.3, 1.8 Hz, 1 H), 4.81 (dd, *J* = 6.6, 6.3 Hz, 1 H), 5.42 (d, *J* = 6.6 Hz, 1 H), 6.43 (br. t, *J* = 2.0 Hz 1 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 19.6 (t), 22.6 (t), 40.0 (t), 41.1 (d), 58.0 (d), 74.0 (d), 74.9 (d), 76.1 (d), 151.4 (s), 156.2 (s).

(+)-4a,5-Dihydro-3-epistreptazoline [(+)-22]: Methyllithium (2.7 mL, 1.6 M in ether, 4.4 mmol, 7.0 equiv.) was added at 0 °C to a solution of anhydrous $ZnBr_2$ (1.12 g, 4.98 mmol, 8.0 equiv.) in THF (5 mL). After 15 min at room temp., a solution of (+)-**21b** (0.20 g, 0.62 mmol) in DMF (10 mL) was added dropwise; 10 min later $Pd(PPh_3)_4$ (22 mg, 19 μmol, 0.03 equiv.) was added, and the reaction mixture was heated at 45 °C. After 1 h, the reaction mixture was cooled to room temp. and poured into a cold saturated aqueous solution of NH_4Cl and extracted with AcOEt. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/EtOH: 95:5) to give 65 mg (50%) of (+)-**22** as a slightly yellow solid. − m.p. 149 °C. − $[\alpha]_D^{20}$ = +78 (*c* = 0.33, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3374, 1708, 1671, 1300, 1254, 1158, 1067, 1013 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 1 H), 1.60 (m, 1 H), 1.80 (m, 1 H), 1.93 (m, 3 H), 2.08 (m, 1 H), 2.46 (m, 1 H), 2.52 (br. s, 1 H, OH), 2.81 (ddd, *J* = 15.3, 12.0, 3.5 Hz, 1 H), 3.80 (m, 1 H), 4.10 (dd, *J* = 7.0, 5.5 Hz, 1 H), 4.67 (br. s, 1 H), 4.77 (dd t, *J* = 7.0, 6.6 Hz, 1 H), 5.52 (tdd, *J* = 7.0, 2.5, 2.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.0 (q), 19.1 (t), 21.5 (t), 37.7 (d), 41.0 (t), 57.4 (d), 74.6 (d), 75.3 (d), 123.4 (d), 136.3 (s), 156.3 (s). − MS (EI): *m*/*z* (%) = 209 (100) [M$^+$], 194 (83), 164 (64), 150 (100), 122 (27), 95 (41), 79 (29), 67 (26), 55 (28). − HRMS (CI$^+$, CH_4); $C_{11}H_{16}NO_3$ [MH$^+$]: calcd. 210.1130; found 210.1129.

(5*S*,6*Z*,7*S*,8*S*,11*S*)-6-Benzylidene-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(−)-(23)]: This compound was prepared by cross-coupling of (+)-**21a** (150 mg, 0.467 mmol) with phenylzinc bromide [prepared from phenyllithium (1.65 mL, 2 M in cyclohexane/ether: 70:30, 3.28 mmol, 7.0 equiv.) and $ZnBr_2$ (0.85 g, 3.77 mmol, 8.1 equiv.) in THF (3.5 mL)], catalyzed by $Pd(PPh_3)_4$ (16 mg, 14 μmol, 0.03 equiv.) in DMF (7.5 mL) as described above. Flash chromatography (CH_2Cl_2/EtOH: 95:5) afforded 95 mg of a

yellow solid, which was washed with benzene to give 74 mg (58%) of (−)-**23** as a white solid. − m.p. 222 °C. − $[\alpha]_D^{20} = -118$ (c = 0.47, CH_3CN). − IR (KBr): $\tilde{\nu}$ = 3530, 1730, 1260, 1020, 1000 cm^{-1}. − ^1H NMR (CD_3CN): δ = 1.19−1.43 (2 H), 1.74 (m, 1 H), 2.05 (m, 1 H), 2.62 (ddd, J = 15.8, 12.1, 3.7 Hz, 1 H), 2.83 (m, 1 H), 3.43 (m, 1 H), 3.44 (d, J = 3.9 Hz, 1 H, OH), 4.07 (dd, J = 7.3, 5.7 Hz, 1 H), 4.26 (d, J = 3.9 Hz, 1 H), 4.47 (d, J = 7.3 Hz, 1 H), 6.34 (m, 1 H), 7.05−7.25 (5 H). − ^{13}C NMR (CD_3CN): δ = 19.7 (t), 21.2 (t), 40.9 (d), 41.4 (t), 58.6 (d), 76.4 (d), 82.4 (d), 126.3 (d), 128.5 (d), 128.9 (d), 129.4 (d), 129.5 (d), 129.6 (d), 137.6 (s), 141.9 (s), 156.7 (s). − MS (EI): m/z (%) = 271 (32) [M^+], 227 (90), 226 (100), 184 (33), 129 (34), 128 (36), 115 (44), 91 (53). − HRMS (CI^+, CH_4); $C_{16}H_{18}NO_3$ [MH^+]: calcd. 272.1287; found 272.1283.

(5*S*,6*Z*,7*S*,8*S*,11*S*)-7-Hydroxy-6-(prop-2-enylidene)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one [(−)-(24)]: This compound was prepared by cross-coupling of (+)-**21a** (164 mg, 0.511 mmol) with vinylzinc bromide [prepared from vinylmagnesium chloride (2.60 mL, 1.68 M in THF, 4.37 mmol, 8.5 equiv.) and $ZnBr_2$ (1.20 g, 5.33 mmol, 10.4 equiv.) in THF (4 mL)], catalyzed by $Pd(PPh_3)_4$ (22 mg, 19 μmol, 0.04 equiv.) in DMF (8 mL) as described above. Flash chromatography (CH_2Cl_2/EtOH, 95:5) afforded 91 mg of a yellow solid, which was recrystallized from *n*-hexane/AcOEt to give 70 mg (62%) of (−)-**24** as a white solid. − m.p. 144−146 °C. − $[\alpha]_D^{20} = -67$ (c = 0.4, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3420, 1710, 1270, 1240, 1060, 1025, 1000 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.41−1.59 (2 H), 1.88 (m, 1 H), 2.16 (m, 1 H), 2.79 (ddd, J = 15.6, 11.6, 4.2 Hz, 1 H), 3.02 (d, J = 3.3 Hz, 1 H, OH), 3.05 (br. s, 1 H), 3.78 (m, 1 H), 4.23 (dd, J = 7.4, 5.7 Hz, 1 H), 4.74 (d, J = 7.4 Hz, 1 H), 4.82 (br. s, 1 H), 5.20 (d, J = 9.9 Hz, 1 H), 5.28 (d, J = 16.9 Hz, 1 H), 6.02 (dd, J = 11.0, 1.8 Hz, 1 H), 6.61 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 18.9 (t), 20.9 (t), 39.2 (d), 40.7 (t), 59.1 (d), 75.4 (d), 81.4 (d), 119.6 (t), 128.5 (d), 132.1 (d), 141.2 (s), 155.7 (s). − MS (EI): m/z (%) = 221 (80) [M^+], 149 (79), 148 (99), 134 (88), 118 (83), 117 (100), 91 (78), 79 (93), 77 (72). − HRMS (CI^+, CH_4); $C_{12}H_{16}NO_3$ [MH^+]: calcd. 222.1130; found 222.1129.

X-ray Crystallographic Study of (−)-4a,5-Dihydrostreptazolin: Colorless single crystals were grown from benzene; crystal shape: parallelepiped; crystal data: molecular formula $C_{11}H_{15}O_3N$; molecular mass: 209.25; temperature 295 K; crystal system: orthorhombic; space group: $P2_12_12_1$; unit cell dimensions: a = 6.140(2) Å, b = 11.347(3) Å, c = 14.714(3) Å, α = 90°, β = 90°, γ = 90°; volume 1025.1(5) Å^3; Z = 4; density (calculated): 1.356 g·cm^{-3}; linear absorption coefficient: μ = 0.92 cm^{-1}. Diffractometer: CAD4 Enraf−Nonius; radiation used Mo-K_α (λ = 0.71069 Å); scan mode ω/2θ; scan range 0.8+0.345 tg θ; θ range for data collection 1° to 28°; number of data collected: 1463; number of unique data used for refinement: 957 $(F_0)^2 > 1.5\sigma(F_0)^2$; final R indices: R = 0.0561, Rw = 0.0648; absorption correction: none; secondary extinction coefficient: 333.02; goodness of fit: S = 1.10; number of variables: 138; Δρ min. − 0.254 e$Å^{-3}$, Δρ max = 0.439 e$Å^{-3}$.
Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136167. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

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