Highly Selective Synthesis of a 2-Deoxyxylonolactam *via* Enantioselective Carbon-Hydrogen Insertion Reactions Using Chiral Dirhodium(II) Carboxamidates

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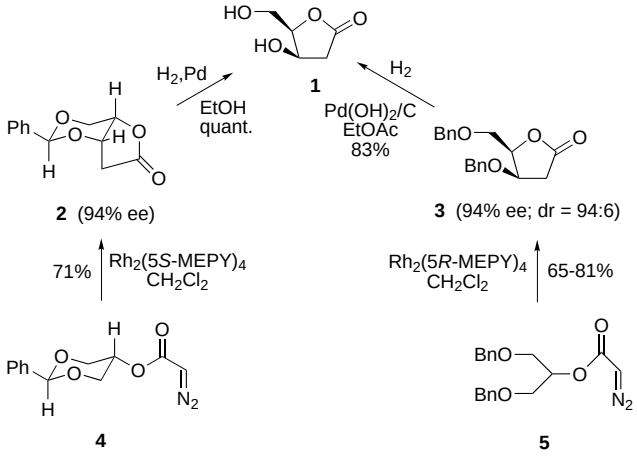
Received October 12, 2001; Accepted November 11, 2001

Abstract: *N*-Benzyl-2-deoxyxylonolactams are accessible by highly chemoselective, diastereoselective, and enantioselective carbon-hydrogen insertion reactions of diazoacetamides. Competing aromatic cycloaddition or β-lactam formation *via* carbon-hydrogen insertion into a benzylic position can be minimized by the proper selection of chiral catalyst. Conformational influences are important in product preference.

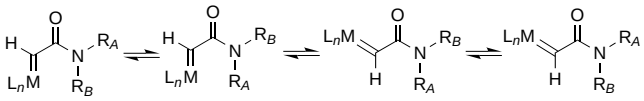
Keywords: aromatic cycloaddition; carbon-hydrogen insertion; chiral dirhodium(II) carboxamidates; conformation; diazoacetamides.

Introduction

We have reported facile syntheses of 2-deoxyxylono-1,4-lactone in both enantiomeric forms *via* highly diastereoselective and enantioselective carbon-hydrogen insertion reactions of diazoacetates (Scheme 1).[1,2] Originally acyclic **5** was employed,[1] but the production of a diastereomeric mixture of **3** prompted us to examine **4** as a precursor and, indeed, diastereomerically pure (4*S*,5*S*)-(−)-2-deoxyxylonolactone **1** could be formed by this methodology in high yield and enantiomeric excess.[2] The major surprise from this outcome was the formation of **2**, suggesting preferential insertion into an axial C–H bond, since with other six-membered ring systems insertion into an equatorial carbon-hydrogen bond occurred to the exclusion of insertion into the axial carbon-hydrogen bond.[3-7] The lactam analogue of **1** was targeted to determine the scope of this methodology. We and others have previously reported C–H insertion reactions leading to lactam products[8] so there is broad understanding of the challenges for conformational control in product selection with this methodology (Scheme 2).[9]



Scheme 1.



Scheme 2.

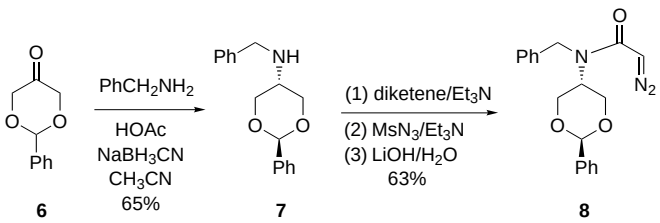
Results and Discussion

Reductive amination of 1,3-dioxanone **6**[10] with sodium cyanoborohydride in the presence of benzylamine gave **7** in good yield after column chromatography and crystallization (Scheme 3).

Attempts to prepare **8** using succinimidyl diazoacetate[9] or through the Corey-Myers/House procedure[11] failed to yield the desired compound, but the three-step procedure using ketene condensation/diazo transfer/deacetylation[8] was successful, and diazoacetamide **8** was formed in 41% overall yield from **6.**

Treatment of diazoacetamide **8** with $Rh_2(OAc)_4$ in dichloromethane resulted in a mixture of C–H insertion product **9** and aromatic cycloaddition product **10** in a 43:57 product ratio (Scheme 4).

The stereochemistry of **9** was ascertained by spectral analyses and the X-ray structure of a crystal grown from dichloromethane/hexanes (Figure 1 and Table 1). This compound was isolated from the reaction mixture as a white crystalline solid in 22% yield. Removal of the benzylidene



Scheme 3.

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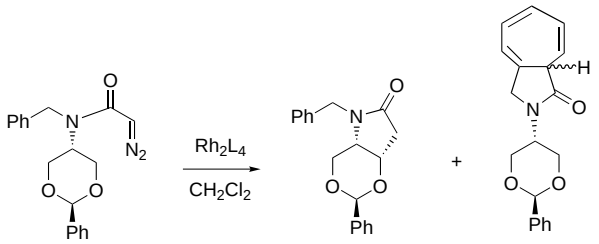


8 9 10

Scheme 4.

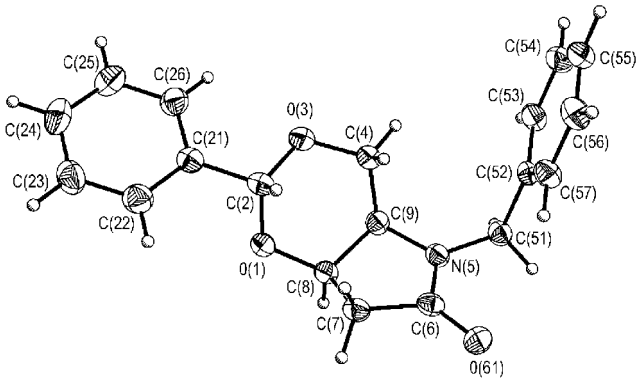


Figure 1. X-ray crystal structure of **9** from reaction with Rh_2(4*S*-MEPY)$_4$ demonstrating the *cis*-ring fusion.

Table 1. Selected bond lengths [Å] and angles [°] for **9.**

O(1)-C(2)	1.412(2)	C(2)-O(3)-C(4)	109.85(16)
O(1)-C(8)	1.433(2)	O(3)-C(4)-C(9)	110.00(16)
C(2)-O(3)	1.410(2)	C(6)-N(5)-C(9)	113.59(17)
C(2)-C(21)	1.500(3)	C(6)-N(5)-C(51)	123.00(17)
O(3)-C(4)	1.431(2)	C(9)-N(5)-C(51)	122.84(16)
C(4)-C(9)	1.521(3)	O(61)-C(6)-N(5)	125.2(2)
N(5)-C(6)	1.353(3)	O(61)-C(6)-C(7)	126.34(19)
N(5)-C(9)	1.457(3)	N(5)-C(6)-C(7)	108.45(17)
N(5)-C(51)	1.461(3)	C(6)-C(7)-C(8)	102.66(16)
C(6)-O(61)	1.231(2)	O(1)-C(8)-C(7)	116.44(17)
C(6)-C(7)	1.510(3)	O(1)-C(8)-C(9)	113.58(16)
C(7)-C(8)	1.526(3)	C(7)-C(8)-C(9)	103.99(16)
C(8)-C(9)	1.541(3)	N(5)-C(9)-C(4)	112.61(16)
C(2)-O(1)-C(8)	114.40(15)	N(5)-C(9)-C(8)	101.42(15)
O(3)-C(2)-O(1)	110.59(16)	C(4)-C(9)-C(8)	111.65(17)
O(3)-C(2)-C(21)	109.90(17)	N(5)-C(51)-C(52)	113.45(17)
O(1)-C(2)-C(21)	107.55(16)		

protective group from **9** was easily effected with Amberlite IR-120 resin (H^+) in a boiling mixture of water and enough dioxane to dissolve **9**; attempted hydrogenolysis at 35 psi using Pd/C was unsuccessful. There was no evidence of the *trans* diastereomer of **9** from reactions catalyzed by $Rh_2(OAc)_4$, nor were the β-lactam products from C–H insertion into the benzylic position observed.

There are three challenges to be overcome in these reactions. One is chemoselectivity in directing product formation to **9** rather than **10.** A second is diastereoselectivity in forming **9**, which with $Rh_2(OAc)_4$ catalysis is the sole stereoisomer. The third challenge is enantioselectivity and, to this end, we

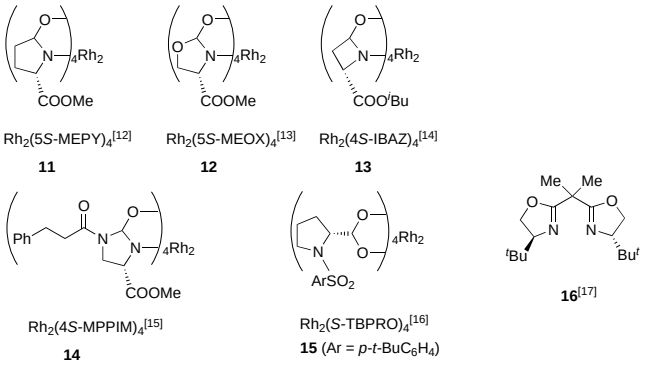
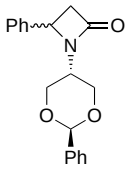


Figure 2. Catalysts used for diazo decomposition of **8**

examined the reactions of **8** with a series of representative catalysts (Figure 2). As with $Rh_2(OAc)_4$, catalysts were employed at 1 mol %, and the results for these reactions are reported in Table 2. Note that with catalysts other than Rh_2(5*S*-MEPY)$_4$ and Rh_2(*S*-TBPRO)$_4$, β-lactam C–H insertion product **17** (Scheme 5) was formed in ratios that are catalyst



17

Scheme 5.

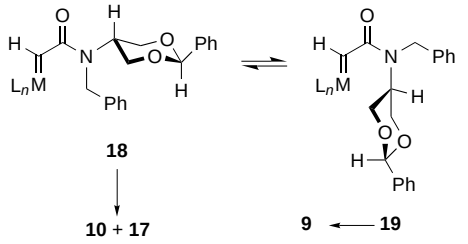
Table 2. Product distribution from catalytic diazo decomposition of diazoacetamide **8** in refluxing dichloromethane.[a]

Catalyst	relative yield[b]			yield	% ee
	9	**10**	**17**	[%] of **9**[c]	**9** [d]
$Rh_2(OAc)_4$	43	57	0	22	–
Rh_2(5*S*-MEPY)$_4$ (**11**)	95	5	0	75	85
Rh_2(4*S*-MEOX)$_4$ (**12**)	74	16	10	61	78
Rh_2(4*S*-IBAZ)$_4$ (**13**)	49	35	16	45	19
Rh_2(4*S*-MPPIM)$_4$ (**14**)	53	18	29	48	37
Rh_2(*S*-TBPRO)$_4$ (**15**)	22	78	0	9	56

[a] Reactions were performed with 1.0 mol % of catalyst.
[b] Determined by ^{1}H NMR analysis of the reaction mixture using the characteristic absorptions of each compound.
[c] Isolated weight yield following chromatographic separation on silica gel (3% EtOAc in CH_2Cl_2).
[d] Enantiomer separation was achieved by HPLC on a Diacel-Chiralpak AD column (*i*-PrOH:hexanes = 10:90). All catalysts gave major enantiomer having the same configuration.

dependent. Obviously, the use of Rh_2(5*S*-MEPY)$_4$ meets all three challenges better than any other catalyst and in excellent yield. Chemoselectivity is very high, diastereocontrol is complete, and enantioselectivity is respectable. The only copper(I) catalyst employed, that derived from bis-oxazoline **16** and $Cu(MeCN)_4PF_6$, gave a 44:47:9 mixture of **9**:**10**:**17.**

What is so very striking about these results is the significant differential in product formation due to catalyst ligands.



Scheme 6.

Increasing the reactivity of the catalyst gives increased contribution from aromatic cycloaddition but a decreased relative amount of β-lactam **17** [Table 1: $Rh_2(OAc)_4$ and Rh_2(*S*-TBPRO)$_4$ > **11** – **14**] with Rh_2(5*S*-MEPY)$_4$ being the exception in its high chemoselectivity. We had anticipated that the relative rates for formation of **9** and **10/17** would be dependent, at least in part, with the equilibrium concentrations of **18** and **19** (Scheme 6). Since this equilibrium changes as a function of temperature, we also determined product ratios for this catalytic reaction in refluxing 1,2-dichloroethane (bp 82 °C) with most of the same catalysts reported in Table 2, and these results are given in Table 3. As can be seen from the data,

Table 3. Product distribution from catalytic diazo decomposition of diazoacetamide **8** in refluxing 1,2-dichloroethane.[a]

Catalyst	**9**	**10**	**17**	**Δ (10 + 17)**[b, c]
$Rh_2(OAc)_4$	54	46	0	−11
Rh_2(5*S*-MEPY)$_4$ (**11**)	67	33	0	+28
Rh_2(4*S*-MEOX)$_4$ (**12**)	69	21	10	+5
Rh_2(4*S*-IBAZ)$_4$ (**13**)	25	47	28	+24
Rh_2(4*S*-MPPIM)$_4$ (**14**)	42	50	8	+11

[a] Reactions were performed with 1.0 mol % of catalyst.
[b] Determined by ^{1}H NMR analysis of the reaction mixture using the characteristic absorptions of each compound.
[c] Difference in relative yield between reaction performed in refluxing dichloroethane and that performed in dichloromethane.

there is a trend to a near 50:50 mixture of **9** and (**10** + **17**) at 82 °C and, except with Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*S*-IBAZ)$_4$, there is no significant change in preference for **9** at that temperature. These results demonstrate that catalyst ligands play a subtle but important role in orienting the metal carbene to a conformation through which insertion or addition takes place, and that conformational influences (Scheme 6) are very important in effecting chemoselectivity.

Conclusions

The application of chiral dirhodium(II) carboxamidates to catalyze diazo decomposition and subsequent carbon-hydrogen insertion from diazoacetamides is a formidable task. Competing reactions, due in part to conformational restrictions of the amide bond, complicate the process. However, use of Rh_2(5*S*-MEPY)$_4$ with diazoacetamide **8** results cleanly in the formation of δ-lactam product **9**, whose stereochemistry is that of a 2-deoxyxylonolactam. Preferential insertion apparently occurred into an axial carbon-hydrogen bond of the reactant, and enantioselection was 85%. With other dirhodium(II) catalysts competition between γ-C–H insertion, aromatic cycloaddition, and β-C–H insertion was of major importance.

Experimental Section

General Remarks

The dichloromethane used in diazo decomposition reactions was distilled prior to use from calcium hydride; all other solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal Me_4Si (TMS). Mass spectra were recorded in the FAB mode. Methanesulfonyl azide was prepared by reaction of methanesulfonyl chloride with sodium azide and was not distilled.[18] Both dirhodium(II) acetate and copper(I) hexafluorophosphate[19] were crystallized prior to use. The preparation of enantiopure catalysts Rh_2(5*S*-MEPY)$_4$,[12] Rh_2(4*R*-MEOX)$_4$,[13] Rh_2(4*S*-IBAZ)$_4$,[14] Rh_2(4*S*-MPPIM)$_4$[15] and bis(oxazoline) copper(I) catalyst[20] have previously been reported. 1,3-Dioxanone **6** was prepared as previously described.[10]

Preparation of *trans*-5-(*N*-Benzylamino)-2-phenyl-1,3-dioxane (7)

To ketone **6** (1.50 g, 8.40 mmol) in acetonitrile (50 mL), was added benzylamine (1.84 mL, 1.80 g, 16.8 mmol) and the mixture was stirred for 15 min. Glacial acetic acid (0.48 mL, 0.50 g, 8.40 mmol) followed by sodium cyanoborohydride (2.11 g, 33.6 mmol) were then added, and the resulting white suspension was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (25 mL) and diluted with dichloromethane (50 mL). The aqueous layer was washed with dichloromethane (2 × 25 mL), and the combined organic layer was washed with water (2 × 25 mL), dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give a clear oil. Purification by column chromatography on silica gel [hexanes:ethyl acetate (4:1) as eluent] afforded the title compound as a white solid; yield: 1.46 g (5.46 mmol, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 – 7.20 (comp, 10H, 2 × C_6H_5), 5.39 (s, 1H, 2-H), 4.32 (dd, 2H, J = 10.5 Hz, 4.0 Hz, 4- and 6-H_{eq}), 3.83 (s, 2H, PhCH_2), 3.52 (t, 2H, J = 10.5 Hz, 4- and 6-H_{ax}), 3.11 (sept, 1H, J = 4.0 Hz, 5-H), 1.37 (s, 1 H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.81, 137.82, 128.78, 128.42, 128.42, 127.89, 127.19, 125.94, 101.21, 71.69, 51.23, 49.61.

Preparation of *trans*-5-(*N*-Benzyldiazoacetamido)-2-phenyl-1,3-dioxane (8)

To amine **7** (1.05 g, 3.95 mmol) in tetrahydrofuran (100 mL) at 0 °C was added diketene (0.92 mL, 1.00 g, 11.9 mmol) followed by triethylamine (3 drops), and the mixture was stirred for 1 h. The reaction solution was then allowed to warm to room temperature and stirred overnight. To the resulting brown reaction mixture was added triethylamine (1.65 mL, 1.20 g, 11.9 mmol) followed by methanesulfonyl azide (1.44 g, 11.9 mmol), and the resulting solution was stirred overnight after which the solvent was removed under reduced pressure to reveal a brown solid. After dilution with dichloromethane (50 mL) and washing with water (2 × 50 mL), the solution was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow oil. Column chromatography with dichloromethane yielded a yellow solid (1.20 g, 3.16 mmol, 80%) which was dissolved in tetrahydrofuran (25 mL). To this solution lithium hydroxide (0.27 g, 11.1 mmol) was added as a solution in water (25 mL) and the resulting orange brown mixture was stirred vigorously for 5 h, after which the reaction was diluted with dichloromethane (50 mL) and the organic layer was washed with water (2 × 25 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a yellow oil. Crystallization

from hexanes-benzene (few drops) afforded the title compound as a yellow solid; yield: 0.83 g, 2.46 mmol, 78%; 63% overall from the amine **7**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.20 (10H, m, 2 × C_6H_5), 5.41 (1H, s, 2-H), 4.97 (1H, s, C*H*N_2), 4.41 (2H, s, $PhCH_2$), 4.32 – 4.09 (5H, m, 4-H_2, 5-H and 6-H_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.0, 137.5, 129.0, 128.9$_6$, 128.2, 127.8, 126.2, 126.0, 101.1, 67.9, 51.1, 47.7; HRMS (FAB): calcd. for $C_{19}H_{20}N_3O_3^+$: 338.1505; found 338.1514.

General Procedure for Diazo Decomposition

To a solution of catalyst (1 mol %) in the indicated solvent (5 mL) at reflux was added the diazoacetamide (50.0 mg, 0.15 mmol) in the same solvent (5 mL) *via* a syringe pump over a 2 h period. After addition of the diazoacetamide was complete, the reaction solution was stirred for an additional 5 min, and then the solvent was removed under reduced pressure, and the mixture was analyzed by ^{1}H NMR spectroscopy. Silica-gel column chromatography (3% ethyl acetate in dichloromethane) yielded the C–H insertion product as a clear oil which solidified on standing. This mixture was then analyzed by HPLC on a Chiralpak AD column with a flow rate of 1.5 mL/min and a solvent mixture of 2-propanol to hexanes (10:90). ^{1}H NMR spectroscopy was used to determine the ratio of C–H insertion (**9**) to aromatic cycloaddition (**10**) products from the signals at δ = 2.82 and 2.66 ppm (both 1H, dd) for the C-H insertion product and at δ = 3.10 ppm (1H, s) for the aromatic cycloaddition product.

For **9**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.60 – 7.23 (10H, comp, 2 × C_6H_5), 5.85 (1H, s, 2-H), 4.85 (1H, d, J = 15 Hz, PhCH_2), 4.59 (1H, dd, J = 13 Hz, 5 Hz, 6-H), 4.22 (1H, d, J = 15 Hz, PhCH_2), 4.01 (1H, dd, J = 12 Hz, 5 Hz, 4-H), 3.74 (1H, dd, J = 12 Hz, 7 Hz, 4-H), 3.61 (1H, dd, J = 12 Hz, 7 Hz, 5-H), 2.82 (1H, dd, J = 17 Hz, 5 Hz, 3′-H_{ax}), 2.66 (1H, J = 17 Hz, 7 Hz, 3′-H_{eq}); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 172.6, 137.2, 136.1, 128.9, 128.8, 128.4, 128.1, 127.9, 126.2, 95.6, 65.9, 62.8, 53.9, 44.7, 35.3; mp 132 – 134 °C; IR (film): ν = 1686 cm^{-1}. HRMS (FAB): calcd. for $C_{19}H_{20}NO_3^+$: 310.1443; found 310.1443. This product formed with the use of Rh_2(4*R*-MEAZ)$_4$ gave **9** having the configuration opposite to that from use of the *S*-configured catalysts reported in Table 2: $[\alpha]_D^{23}$: – 5.1 ($CHCl_3$, *c* 0.47) for 52% ee (HPLC, Chiralpak-AD column).

For **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 – 7.47 (2H, comp, Ph-H), 7.39 – 7.35 (3H, comp, Ph-H), 6.50 (2H, t, J = 4.0 Hz, 6′-H and 7′-H), 6.17 (2H, m, 4′-H and 5-H), 5.26 (1H, dd, J = 3.5 Hz, 9.5 Hz, 8′-H), 5.52 (1H, s, 2-H), 4.38 – 4.47 (1H, m, 5-H), 4.31 – 4.25(4H, comp, 4-H and 6-H), 4.13 (1H, d, J = 11 Hz, 1′-H), 4.09 (1H, d, J = 11 Hz, 1′-H), 3.10 (1H, s, 10′-H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 174.6, 137.3, 130.6, 129.7, 129.0, 128.7, 128.3, 127.1, 126.1, 120.4, 119.9, 101.1, 66.97, 66.91, 49.0, 46.0, 45.8; IR (film): ν = 1686 cm^{-1}; mp 130 – 132 °C. HRMS (FAB): calcd. for $C_{19}H_{20}NO_3^+$: 310.1443; found 310.1446.

For **17**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 – 7.31 (10H, comp, Ph-H), 5.38 (1H, s, 2-H), 4.56 (1H, dd, J = 2.5 Hz, 5.0 Hz, 2′-H), 4.11 – 4.29 (3H, comp, 4-H and 6-H_{eq}), 3.91 (1H, t, J = 11 Hz, 6-H_{ax}), 3.67 – 3.72 (1H, m, 5-H), 3.36 (1H, dd, J = 5.5 Hz, 15 Hz, 3′-H), 2.90 (1H, dd, J = 2.5 Hz, 15 Hz, 3′-H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 167.3, 138.3, 137.3, 129.2, 129.0, 128.2, 126.4, 125.9, 101.2, 67.9, 67.7, 54.0, 47.8, 46.5; IR (film): ν = 1746 cm^{-1}. HRMS (FAB): calcd. for $C_{19}H_{20}NO_3^+$: 310.1443; found 310.1444.

Crystal Structure (2*S*,4a*S*,7a*S*)-5-Benzyl-2-phenyltetrahydro[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (9)

A colorless block from the reaction of Rh_2(5*S*-MEPY)$_4$ of $C_{27}H_{24}N_2O_4$ having approximate dimensions of 0.10 × 0.17 × 0.17 mm. Examination of the crystal on a Bruker SMART 1000 CCD detector X-ray diffractometer at 170(2) K and a power setting of 50 KV, 40 mA showed measurable diffraction to at least θ = 26.03°. Data were collected using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Initial cell constants and an orientation matrix for integration were determined from reflections obtained in three orthogonal 5° wedges of reciprocal space. A total of 3736 frames at 1 detector setting covering 0 < 2θ < 60° were collected, having an ω-scan width of 0.2 and an exposure time of 30 seconds. The frames were integrated using the Bruker SAINT software package's narrow frame algorithm. A total of 22795 reflections were integrated and retained of which 4624 were unique (⟨redundancy⟩ = 4.9, R_{int} = 14.8%, R_{sig} = 20.8%). Of the unique reflections, 1641 (35%) were observed > 2σ(I). The absorption coefficient is 0.090 mm^{-1} and no absorption corrections were applied. The final cell parameters: monoclinic, space group *P*2(1)/*n* with *a* = 11.131(2) Å, *b* = 16.910(4) Å, *c* = 12.432(3) Å, beta = 109.575(4)°, volume = 2204.8(8) Å^3, Z = 4, ρ_{calc} = 1.3275 g/cm^3, F(000) = 928. The structure was solved using SHELXS in the Bruker SHELXTL (Version 5.0) software package.[18] Solution was achieved utilizing direct methods followed by Fourier synthesis. Hydrogen atoms were located in the difference map and given thermal parameters equal to 1.2 times U_{iso} of that bonded atom; their positions were refined. The final anisotropic full-matrix least squares refinement based on F^2 of all reflections converged (maximum shift/esd = 0.004) at R1 = 0.2212, wR2 = 0.1978 and goodness-of-fit = 0.919. Conventional refinement indices using the 1641 reflections with F > 4σ(F) are R1 = 0.0591, wR2 = 0.1366. The model consisted of 370 variable parameters. Highest peak: 0.303 e/Å^3 located 1.15 Å from O22.[19] Lowest peak: – 0.320 e/Å^3 located 0.94 Å from C22.[19]

Deprotection of the Lactam 9

To a solution of the lactam (50 mg, 0.162 mmol) in a mixture of dioxane and water (1:1, 10 mL) was added Amberlite IR-120 (H^+) resin (150 mg) and the mixture was heated at reflux for 4 h. The mixture was then allowed to cool to room temperature, and the resin was filtered off and washed with methanol. The solvent removed under reduced pressure to yield the crude product which was recrystallized from dichloromethane:hexanes to yield the corresponding diol (11 mg, 32%) which was an exact match to the same compound reported by Takahata[20]: ^{1}H NMR [500 MHz (CD_3)$_2$CO]: δ = 7.30 – 7.20 (5H, comp), 4.98 (1H, d J = 15 Hz), 4.85 (1H, s), 4.47 – 4.43 (1H, m), 4.15 (1H, d, J = 15 Hz), 3.82 (1H, d, J = 4 Hz), 3.53 – 5.49 (1H, m), 2.66 (1H, dd, J = 17 Hz, 7 Hz), 2.49 (1H, dd, J = 17 Hz, 5 Hz).

Acknowledgements

Support for this research by the National Science Foundation and the National Institutes of Health (Grant GM 46503) to M.P.D. is gratefully acknowledged. The authors acknowledge the Molecular Structure Laboratory at the University of Arizona and NSF grant CHE-9610374 which provided the diffractometer. The 500 MHz NMR spectrometer was purchased through a grant received from the NSF (CHE-9729350).

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[19] CCDC-172931 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk)..
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