Development of the Carbocyclic Nucleoside MDL 201449A: A Tumor Necrosis Factor- α Inhibitor

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Abstract:

An efficient synthesis of (1S,4R)-(-)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenyl acetate and (1R,4S)-(-)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenol is described utilizing a furfuryl alcohol rearrangement, followed by a lithium aluminum hydride reduction with high facial selectivity and an efficient enzymatic resolution with pancreatin. Both of these intermediates were successfully utilized in the preparation of the carbocyclic nucleoside 9N-[(1'R,3'R)-*trans*-3'-hydroxycyclopentanyl]adenine hydrochloride, an agent which inhibits the formation of tumor necrosis factor- α .

Introduction

The overproduction of the proinflammatory cytokine, tumor necrosis factor- α (TNF- α), has been directly linked to multiple-organ diseases.¹ Such diseases include septic shock, adult respiratory distress syndrome, AIDS, inflammatory bowel disease, bacterial meningitis, malaria, multiple sclerosis, atherosclerosis, and rheumatoid arthritis to name a few.¹ The carbocyclic nucleoside 9*N*-[(1'*R*,3'*R*)-*trans*-3'hydroxycyclopentanyl]adenine hydrochloride, (MDL 201449A, 1) has been shown to inhibit the production of TNF- α , thus



having potential for the treatment of multiple inflammatory diseases.¹ It became necessary to develop a synthesis for preparing larger quantities of MDL 201449A that would provide 2 kg for preliminary toxicological studies.

(1) (a) Edwards, C. K., III; Borcherding, S. M.; Zhang, J.; Borcherding, D. B. The Role of Tumor Nercosis Factor-α in Acute and Chronic Inflammatory Responses: Novel Therapeutic Approaches. In *Xenobiotics and Inflammation*; Schook, L. B., Laskin, D. L., Eds.; Acedemic Press: New York, 1994; pp 97–136. (b) Borcherding, D. R.; Peet, N. P.; Munson, R.; Zhang, H.; Hoffman, P. F.; Bowlin, T. L.; Edwards, C. K., III. *J. Med. Chem.* **1996**, *39*, 2615–2620.

Scheme 1. Retrosynthetic analysis



Retrosynthetically, one can envision a disconnection between the *N9* position of the adenine portion and the cyclopentanol ring of **1**, as shown in Scheme 1. The coupling of adenine **2** to a differentially protected cyclopentadiol **A** can be accomplished via $S_N 2$ displacement to give the desired *R*,*R* chirality in product **1**. Therefore, the 1,3disubstituted cyclopentane ring must be *cis* in nature, as displayed in enantiomer **A**. These 1,3-*cis*-disubstituted cyclopentane systems can be easily obtained through reduction of *cis*-2-cyclopentene-1,4-diol derivatives **B**. Previous preparations of many *cis*-2-cyclopentene-1,4-diol derivatives proved costly, lengthy, or difficult for scaling up.²

The first generation synthesis developed by Discovery Chemistry centered on the preparation of the 2-cyclopentene-1,4-diol derivative **5** shown in Scheme 2. Dicyclopentadiene was cracked and captured with bromine to form a mixture of the *cis*- and *trans*-1,4-dibrominated cyclopentene³ derivatives **3**. This was converted to the diol **5**, which was determined to consist of a 55:45 *cis:trans* mixture. This mixture was desymmetrized enzymatically to produce the desired (1R,4S)-(-)-4-acetoxy-2-cyclopentenol (**6**), which was separated from the diacetate and *trans* diol via chromatography. The olefin was reduced catalytically to (1R,3S)-(-)-1-acetoxycyclopentan-3-ol (**7**), and the free hydroxyl group was converted to the mesylate **8**. Coupling of mesylate **8** with adenine **2** was carried out with sodium hydride to give the acetoxy-protected carbocyclic nucleoside

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^{(2) (}a) Curran, T. T.; Hay, D. A.; Koegel C. P.; Evans, J. C. *Tetrahedron* 1997, 53, 1983. (b) For a complete list of *cis*-2-cyclopentene-1,4-diol derivatives, see ref 1 of ref 2a. (c) Watson, T. J. N. Chemical Development of MDL 201449A. Presentation at the Midwest Pharmaceutical Process Chemistry Consortium, Cincinnati, OH, October 10, 1997. A copy of slides can be obtained from Tim Watson: Hoechst Marion Roussel Research Institute, 2110 E. Galbraith Rd., Cincinnati, OH 45215-6300.

⁽³⁾ Owen, L. N.; Smith, P. N. Alicyclic Glycols 1952, 4035-4047.

Scheme 2. First generation Discovery Chemistry synthesis



9. This was deprotected with acid, yielding MDL 201449A (1) in an overall yield of less than 1% and a chemical purity typically ranging from 90 to 95%.^{1,4}

A critique of the discovery synthesis rendered the following development issues. The cracking of dicyclopentadiene to cyclopentadiene is commonly used to prepare cis-2-cyclopentene-1,4-diol derivatives.² Although the difficulties attributed to this chemistry are not entirely impossible to scale-up, we prefer to avoid them due to some safety issues and patent questions. Bromination of the cyclopentadiene is non-selective and thus yields a *cis:trans* mixture, of which the *trans* portion is rendered useless for the preparation of **1**. The 14% yielding enzymatic desymmetrization of diols 5 using pancreatin is less than desirable, and the use of dichloromethane in the mesylation reaction has environmental constraints. The final deprotection with hydrochloric acid in ethanol, however, was attractive because the product crystallized from the reaction medium and could be easily isolated via filtration.

Some analytical evaluations of the early development samples revealed four major impurities (Figure 1). The enantiomer **10** and the diastereomer **11** presumably come from the contamination of (1R,3S)-(-)-1-acetoxycyclopentan-3-ol (7) with the other possible isomers. Impurities **12** and **13** are the regioisomers generated during the coupling reaction with adenine.^{2c,5a} All four contributed to roughly 5% (best sample) of the total impurities in MDL 201449A and could not be removed without tedious preparative chromatography techniques.

Our efforts concentrated on developing a process that would be cost-effective and easily scaled-up and would



Figure 1. Major impurities.

eliminate the need for preparative chromatography. The details contained within pertain directly to our scale-up efforts and issues encountered during the preparation of multigram quantities of MDL 201449A.^{2,5,6}

Results and Discussion

The route eventually developed to prepare a 1,4-*cis*disubstituted cyclopentene derivative is shown in Scheme $3.^{2a,c,6}$ Both (1S,4R)-(-)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenyl acetate (**17**) and (1R,4S)-(-)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenol (**18**) have the potential to yield

⁽⁴⁾ Borcherding, D. Discovery Chemistry, Hoechst Marion Roussel, private communications.

 ^{(5) (}a) Curran, T. T.; Barbuch, R. B.; Hay, D. A.; Vaz, R. J. *Tetrahedron* 1997, 53, 7181. (b) Curran, T. T.; Hay, D. A. *Tetrahedron: Asymmetry* 1996, 7, 2791.

^{(6) (}a) For a more complete history on route selection and methodology, refer to refs 2 and 5. (b) Curran, T.; Hay, D.; Evans, J. International Patent WO 96/30320, 3 October 1996.



Table 1. Furfuryl alcohol rearrangement



MDL 201449A (1). Their simple synthesis was attractive for preparing the first 2 kg of drug substance.

Following a procedure by Nanni et al.,^{2a,7} furfuryl alcohol could easily be rearranged under acidic conditions to (\pm) -4-hydroxy-2-cyclopentenone (14), in which the oxygen functionalities have the proper regioconfiguration. Our best yield was 53% when the reaction was run under dilute conditions;⁷ furthermore, after more experimentation,^{2a,c} it was found that the yield diminishes at higher concentrations (Table 1). For the most part, the decreased yields were attributed to higher amounts of a visible polymer formed from the furfuryl subunit during the reaction. However, due to the inexpensive furfuryl alcohol⁸ in conjunction with the aqueous reaction medium, we proceeded at a concentration of 2.5-2.8 M in a 30-gal reactor. A cost and time analysis showed that this concentration maximizes the throughput for the desired quantity of 14, which was necessary to expedite the process. Due to time constraints, experimental design to optimize or revise the reaction was not performed.

To provide the desired *cis* configuration in the cyclopentane moiety, reduction of the ketone required high facial selectivity with hydride entering *anti* to the hydroxyl group. Direct reduction of **14** gave low yields, poor isolation, and moderate selectivity, suggesting the need for a protecting group.^{2a,c} A survey of protecting groups revealed the *tert*-butyldimethyl silyl group (TBDMS) to have several advantages.⁶ First, it helped add steric bulk to one face of the molecule, thus increasing facial selectivity during reduction. Second, it increased the overall lipophilicity, thus assisting with isolation. For these reasons, along with time constraints, the TBDMS protecting group was prepared under standard conditions.

The reduction of cyclopentenone 15 was conducted using lithium aluminum hydride (LAH)/lithium iodide (LiI) to give the alcohol 16 with a 39:1:trace ratio of cis:trans:overreduction product resulting from 1,4 addition (followed by 1,2 addition).^{2a,c,6} Lithium iodide reduces the 1,4-addition side product and ultimately permits an increase in reaction temperature from -78 °C (difficult to attain at our facility) to -30 °C, which is readily achievable in our reactor.^{2c} All Lewis acids substituted for LiI proved inferior.^{2a} Although not as efficient as the LAH/Et₂O reducing conditions in terms of *cis:trans* ratio,^{2a} a toluene and *tert*-butyl methyl ether (TBME) solvent system was developed to eliminate the hazards associated with diethyl ether. tert-Butyl methyl ether is an acceptable replacement for diethyl ether and is necessary to solubilize the LAH in a toluene environment (Table 2). The large-scale reduction eventually used 0.54 equiv of LAH and 2.1 equiv of LiI. Due to the apparent handling hazards associated with LAH and desired anhydrous LiI, these raw materials were purchased in preweighed toluene-soluble bags. This is an excellent method of charging hazardous and hygroscopic reagents to minimize exposure and reduce safety issues.^{2c}

Reduction of (\pm) -4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**15**) led to another interesting observation. Cyclopentenone **15** was found to be contaminated with roughly 17% of *tert*-butyldimethylsilanol from the use of excess *tert*-butyldimethylsilyl chloride (TBDMSCI) in the protection step. Although the silanol can be removed by tedious vacuum distillation or an azeotrope with toluene, this was not done on account of the small-scale reactions not being effected from this contaminant. Surprisingly, *tert*-butyldi-

⁽⁷⁾ Nanni, M.; Ta-machi, H.; Moriyama-shi. Japanese Patent Disclosure Bulletin No. 57-62236, 15 April 1982.

⁽⁸⁾ Furfuryl alcohol cost for our campaign was \$2.40/kg.

1,4 over reducti product (majorit <i>cis</i>)	1,4 over reduction product (majority <i>cis</i>) HO OTBDMS					
	conditions	yield (%)	<i>cis:trans</i> :1,4 reduction			
1 equiv of LAH	Et₂O, −78 °C	70	40:1:4			
1 equiv of LAH; 5 equiv of LiI	-20 °C	74	25:1:trace			
0.5 equiv of LAH; 0.5 equiv of LiI	−30 °C	79	24:1:trace			
toluene/TBME 0.5 equiv of LAH; 2 equiv of LiI	−30 °C	75	35-39:1:trace			

Table 3. Silanol contamination: reduction of enone 15

TBDMS-OH	cis:trans ratio
17-20% (~0.5 equiv to LAH)	35-39:1
32%	28:1
0-2.1% (catalytic)	20-24:1
remove LiI (with 17% trimethylsilanol	26:1

methylsilanol clearly had an effect on the facial selectivity observed during the LAH reduction (Table 3). One may speculate that the *tert*-butyldimethylsilanol and LAH form a new bulky reducing species. Why the 17% of *tert*-butyldimethylsilanol gave the optimal *cis:trans* ratio is not fully understood at this time.^{2a}

A survey of resolving conditions for alcohol 16 ultimately led to the selection of the acylation of the free hydroxyl group with vinyl acetate and the enzyme pancreatin.^{2,5} Pancreatin is readily available and is a relatively inexpensive enzyme.⁹ A screening of this enzyme in traditional solvents proved that, by using TBME, both acetate 17 and alcohol 18 were obtained in high enantiomeric excess (Table 4). The use of THF as solvent yielded a undesirably slow resolution time with diminished ee's, while cyclohexane has flammability liability which we wanted to avoid. The increase in lipophilicity of the TBDMS alcohol 16 contributed to much of the enzymatic resolution success in a wide array of ethers and solvents. All changes of the protecting group gave inferior results in the resolution and did not provide exceptional optical purities as obtained in the silvl ether series; such high optical purities of 17 and 18 permitted us to investigate two routes to 1.^{2a,c} Separation of acetate 17 from alcohol 18 was easily accomplished via plug chromatography (see Experimental Section). The kilo-scale reaction did not produce, in terms of yield, the same efficiency as the small laboratory screenings because there were some mixed fractions that were discarded. It should be noted that acetate 17 and alcohol 18 possess different vapor pressures which may afford a separation by distillation for future supplies.2c

All of the intermediates in Scheme 3 were viscous oils. Although acetoxy-TBDMS-protected cyclopentenediol 17 and TBDMS-protected silanol **18** were obtained in high enantiomeric excess, they contained some minor unknown impurities (roughly 95% pure). When analyzed by chiral gas chromatography and GC/MS, they were presumably product related. How these would affect the overall purity of **1** remained unknown.

The most direct path to **1** (route 1, Scheme 4) utilized the TBDMS-protected silanol **18**. While we believe the TBDMS group added versatility, it remained to be determined if this was a sufficient replacement for the efficient acetoxy group which Discovery Chemistry had shown could be efficiently removed with hydrochloric acid to provide **1** from **9** (Scheme 2). Although the acetoxy-TBDMS-protected cyclopentenediol **17** required a selective deprotection step in the process, this chemistry was also proven successful in preparing MDL 201449A (**1**). Both *routes 1 and 2* from Scheme 4 were evaluated and compared.

Route 1. Route 1 is summarized in Scheme 5. Hydrogenation of the TBDMS-protected diol **18** using Raney nickel revealed another obstacle: double bond migration of the olefin. This migration produced ketone **19'** (Table 5) as a side product, resulting in irreproducible and moderate yields of desired **19**. Minimization of the formation of ketone **19'** would clearly affect the throughput of the process. A summary of some catalysts screened is shown in Table 5.^{2a} The catalyst of choice for this process proved to be nickel boride.¹⁰ Nickel boride [P-2], generated from nickel acetate and sodium borohydride in an alcoholic medium, gave reproducible results in high yields with minimum olefin migration. This catalyst was also attractive from a safety perspective because it was significantly less pyrophoric than the other catalysts that were screened.

The mesylate of 19 was easily prepared in TBME replacing the undesired dichloromethane used originally. The coupling conditions of the mesylate of 19 with adenine 2 were restricted due to poor solubility.^{2a,c,5a} Due to time constraints, this coupling was eventually performed with sodium hydride in dimethyl acetamide (DMA) to give the TBDMS-protected MDL 201449A, 20. It was discovered that this compound could be crystallized from methanol. This crystallization removed the TBDMS-protected regioisomers of 12 and 13 (Figure 1). Because of time constraints, a poor coupling and crystallization yield of 34% was tolerated. TBDMS deprotection of MDL 201449A 20 with hydrochloric acid proceeded without incident to provide MDL 201449A (1), which crystallized from the reaction medium. The overall purity of 1 was 96.8%, with the two major impurities being enantiomer 10 and diastereomer 11. These could not be removed via recrystallization of 1 or 20. In fact, the purity profile of **20** directly dictated that of **1**. Nevertheless, 2 kg of 1 was prepared and delivered for preliminary toxicological and safety studies.

Ultimately, the purification issue in route 1 was solved when it was found that the (1R)-(-)-10-camphorsulfonate (CSA) salt of **20** could be prepared and recrystallized to a purity of >98% with no more than 1% each of **10** and **11**

⁽⁹⁾ Pancreatin (American Laboratories Inc.), \$75/kg (8× USP specifications).

^{(10) (}a) Rylander, P. N. Catalytic Hydrogenation in Organic Synthesis; Academic Press: New York, 1979; pp 37–38. (b) Brown, C. A.; Ahuja, V. K. J. Org. Chem. 1973, 38, 2226.

Tak	ole 4	. Pancreatin	resolution	screenings
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enzyme (wt equiv)		solvent		yield (%) (% ee)	
	time (h)		reagents	17	18
pancreatin (3)	26	THF	VA^a (5 equiv), Et ₃ N (0.7 equiv)	46 (96)	48 (98)
pancreatin (3)	7	TBME	VA (5 equiv), Et ₃ N (0.7 equiv)	46 (99)	50 (99)
pancreatin (3)	2	cyclohexane	VA (5 equiv)	50 (99)	44 (98)

 a VA = vinyl acetate.

Scheme 4



Scheme 5. Route 1



(Scheme 6). Interestingly enough, the (S) enantiomer of CSA was also sufficient in carrying out this process. However, it became clear that a crystalline intermediate prior to coupling with adenine 2 could potentially eliminate the need for this purification technique.

Route 2. Route 2 is summarized in Scheme 7. Selective deprotection of the TBDMS group of **17** with tetrabutyl-ammonium fluoride (TBAF) resulted in acetyl migration. Prolonged reaction exposure times involved with scaling-up resulted in excessive acetyl migration, thus forming more of the enantiomer as well as the diacetate and diol, resulting in diminished yields (table in Scheme 7).

Although the deprotection with TBAF was unacceptable, it provided adequate amounts of acetoxy alcohol **6** to explore the scope of route 2. This deprotection problem was eventually solved by selective silyl ether cleavage with hydrochloric acid (1 equiv) at ambient temperature in ethanol. Much to our delight, the acetyl alcohol **6** was found to crystallize from TBME. This crystallization resulted in a chemical purity of >99%, with an optical purity of >99% ee.^{2a,c} The acetyl alcohol **6** was the only solid encountered in the protected cyclopentene–cyclopentanediol series.

Hydrogenation of the acetyl-protected cyclopentenediol 6, not suprisingly, displayed the same olefin migration as the monoprotected TBDMS species (thus, shedding some light on the moderate yields observed in the Discovery Chemistry hydrogenation). Again, nickel boride proved to be the catalyst of choice for this reduction. The mesylate of alcohol 7 was coupled with adenine 2 using chemistry analogous to route 1 to give acetyl-protected 9, which, in turn, was plug chromatographed to minimize the N-3 isomer 12, followed by crystallization from MEK to effect the removal of trace ammounts of the N-3 isomer and further minimize acetyl isomers 12 and 13. Deprotection of 9 with hydrochloric acid proved successful in ultimately preparing 107 g of MDL 201449A (1), with greater than 99% overall purity. The value of the precoupling, crystalline intermediate **6** is clearly reflected in the overall purity of **1**.

Conclusion

Two successful routes to MDL 201449A were developed from both products derived from an efficient enzymatic resolution of TBDMS-protected cyclopentenediol **16**. Both routes eliminated preparative chromatography and proved successful in providing larger amounts of MDL 201449A with purities >98% and ee's >99%. Route 1 utilized a salt purification of the penultimate intermediate TBDMS-



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Scheme 6. CSA purification

 Ni_2B-P2



EtOH (1 atm or 50 psi)

protected **20**, whereas route 2 employed the crystalline properties of acetyl-protected diol **6**. The "cost of the chirality" in MDL 201449A is lowered significantly since furfuryl alcohol is efficiently converted into two useful intermediates, **17** and **18**, in high enantiomeric excess via rearrangement, protection, stereoselective reduction, and resolution.

Although this was a highly efficient two-route process for preparation of MDL 201449A (1), ideally a single process is desired. Furthermore, an initial cost analysis revealed that TBDMSCl was responsible for 39% of the overall cost of $1.^{11}$ Developing a postresolution, recyclable intermediate and replacing the TBDMS protecting group are two areas that could greatly improve the process. Nevertheless, the synthesis described herein provided an expeditious process to larger quantities of MDL 201449A, along with providing valuable insight into future development plans.

Experimental Section

General. NMR spectra were recorded on a Varian XL 300 and/or Varian Gemini-300 spectrometers at 300 MHz for¹H and at 75 MHz for ¹³C.

(±)-4-Hydroxy-2-cyclopentenone (14). A mixture of H₂O (60 L), furfuryl alcohol (15.0 kg, 152.9 mol), and KH₂PO₄ (750 g) was adjusted to a pH of 4.1 by addition of H₃PO₄ and then heated to and maintained at 98 °C. The reaction was monitored by gas chromatography (GC) (injector temperature, 190 °C; detector temperature, 270 °C;

program, 100 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum 10 m \times 0.53 mm \times 2.65 μ m film thickness; $t_{\rm R}$ of furfuryl alcohol = 1.0 min, $t_{\rm R}$ of 14 = 3.6 min). A typical reaction time of 48 h was required. The reaction mixture was cooled to 35 °C and diluted with ethyl acetate (40 L), and the layers were separated. The aqueous layer was extracted with ethyl acetate (30 L), and the combined organic layers were extracted with water (3 \times 10 L). Aqueous extracts were combined and concentrated at 60 °C/50 Torr to give an oil weighing 3.6 kg. The oil was dissolved in THF (16 L), and the resulting solution was dried with $MgSO_4$ (500 g). The drying agent was filtered off and the filter cake was washed with THF (4 L). The filtrate was concentrated at 40 °C/50 Torr to give 2.6 kg of (\pm) -4-hydroxy-2-cyclopentenone (14) as a red oil (17%). ¹H NMR (CDCl₃): δ 7.6 (dd, 1H), 6.2 (d, 1H), 5.0 (dt, 1H), 3.6–3.2 (bs, –OH, 1H), 3.8 (dd, 1H), 2.2 (dd, 1H). Complete analytical data were compared against the control sample reported in ref 2a.

>9:1

 (\pm) -4-tert-Butyldimethylsilyloxy-2-cyclopentenone (15). A mixture of THF (20 L), NEt₃ (9.00 L, 64.5 mol), 14 (4.00 kg, 40.7 mol), and DMAP (100 g) was cooled under nitrogen to 0 °C. tert-Butyldimethylsilyl chloride (5.85 kg, 38.8 mol) was dissolved in THF (5 L) and added to the reaction mixture at such a rate that the reaction temperature did not exceed 0 °C (total addition time was 0.75 h). The reaction mixture was warmed to 25 °C, stirred for 16 h, and monitor by GC (injector temperature, 190 °C; detector temperature, 270 °C; program, 100 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum 10 m \times 0.53 mm \times 2.65 μ m film thickness; t_R of 14 = 3.6 min, t_R of 15 = 2.6 min). The reaction mixture was cooled to 0 $^{\circ}$ C, and H₂O (22 L) was slowly added at such a rate that the temperature of the reaction mixture did not exceed 25 °C. A total of 16 L of 1 N HCl was added, and the mixture was stirred for 30 min. The mixture was then extracted with hexane $(2 \times 40 \text{ L})$. The organic layers were combined, washed with 0.2 N HCl (20 L), saturated NaHCO₃ (12 L), and brine (12 L) and then dried over MgSO₄. Drying agent was filtered off and washed with hexane (5 L). Solvent was removed at 40 °C/100 Torr, followed by distillation of

⁽¹¹⁾ The cost analysis of TBDMSCl was performed in 1995. Since then, bulk suppliers of TBDMSCl have lowered the price.



product at 90 °C/6 Torr to give 6.6 kg (76% yield) of (\pm)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**15**) as a light yellow oil. ¹H NMR (CDCl₃): δ 7.4 (dd, 1H), 6.2 (dd, 1H), 5.0 (dd, 1H), 2.7 (dd, 1H), 2.2 (dd, 1H), 0.95 (s, 9H), 0.05) (s, 6H). ¹³C NMR (CDCl₃): 206.4, 163.8, 134.4, 70.8, 44.9, 25.6, 18.0, -4.6 ppm. MS: *m*/*z* (M⁺) calcd 212, (M + H) obsd 213. Complete analytical data were compared against the control sample reported in ref 2a.

 (\pm) -cis-4-tert-Butyldimethylsilyloxy-2-cyclopentenol (16). Toluene (48 L), LiI (8 kg, 59.7 mol), and LAH (600 g, 15.8 mol) were combined under a nitrogen atmosphere and cooled to -30 °C. A solution of 15 (6 kg, 28.25 mol) in TBME (28 L) was added to the mixture at such a rate that the reaction temperature did not exceed -20 °C. The reaction mixture was stirred at -30 °C for 3 h while the reaction was monitored by GC (injector temperature, 190 °C; detector temperature, 270 °C; program, 100 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum $10 \text{ m} \times 0.53 \text{ mm} \times 2.65 \ \mu\text{m}$ film thickness; t_{R} of 15 = 2.6min, $t_{\rm R}$ of 16 = 2.3 min). The reaction was quenched with saturated NH₄Cl (20 L) at such a rate that the reaction temperature did not exceed 10 °C. The aluminum salts were filtered off and washed with toluene (6 L). The organic layer was separated, and the aqueous layer was extracted with toluene (6 L). All organic extracts were combined and concentrated at 50 °C/100 Torr. The residue was dissolved in ethyl acetate (8 L) and dried over MgSO₄ (500 g). Drying agent was filtered off and washed with ethyl acetate (2 L). The filtrate was evaporated at 50 °C/100 Torr to give 6.4 kg of (\pm) -cis-4-tert-butyldimethylsilyloxy-2-cyclopentenol (16). This compound was used without further purification (76% yield, 96% pure by GC; 37:1 cis/trans) (column, CDX- β 10 m × 0.25 mm; 0.25 μ m, T = 100 °C). ¹H NMR (CDCl₃): δ 6.0 (bd, 1H), 5.9 (bd, 1H), 4.7 (m, 1H), 4.6 (m, 1H), 2.7 (m, 1H), 2.2 (bm, 1H), 1.5 (m, 1H), 0.9 (s, 9H), 0.1 (s, 6H). ¹³C NMR (CDCl₃): 128, 127, 176 (2C's), 44, 26, 18, -4.7 ppm. Complete analytical data were compared against the control sample reported in ref 2a.

(1S,4R)-(-)-4-tert-Butyldimethylsilyloxy-2-cyclopentenyl acetate (17) and (1R,4S)-(-)-4-tert-Butyldimethylsilyloxy-2-cyclopentenol (18). 16 (6.5 kg, 30 mol) and TBME (40 L) were combined and stirred under a nitrogen atmosphere. To the mixture were added Et₃N (2.87 L, 20.6 mol), pancreatin (8× USP grade, 19.5 kg, 3 wt equiv), and vinyl acetate (14 L, 151.9 mol). The mixture was stirred for 7 h while the reaction was monitored using GC (injector temperature, 190 °C; detector temperature, 270 °C; program, 100 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum $10 \text{ m} \times 0.53 \text{ mm} \times 2.65$ μ m film thickness; t_R of 16 = 2.3 min, t_R of 17 = 3.7 min, $t_{\rm R}$ of 18 = 2.3 min). The pancreatin was filtered off and washed with TBME (18 L), and the filtrate was concentrated at 30 °C/50 Torr to give 9.0 kg of crude 17 and 18. The 9 kg was divided into thirds and chromatographed on 12 kg of silica gel (Merck: 230-400 mesh), eluting first with 32 L of heptane, then with 5% ethyl acetate/heptane to collect 17, and finally with 50% ethyl acetate/heptane to collect 18 (TLC 5% ethyl acetate/heptane; R_f of 17 = 0.5, R_f of 18 =0.1). Both fractions were concentrated separately at 40 $^{\circ}C/$ 50 Torr to produce a total (from the three chromatographies) of 2.72 kg of (1S,4R)-(-)-4-tert-butyldimethylsilyloxy-2cyclopentenyl acetate (17, 70% yield, 98% ee) and 2.5 kg of (1R,4S)-(-)-4-tert-butyldimethylsilyloxy-2-cyclopentenol (18, 77% yield, 98.4% ee). Note: conditions for determining % ee of these materials can be found in refs 2a and 5b.

Compound 17. ¹H NMR (CDCl₃): δ 6.0 (bd, 1H), 6.0 (bd, 1H), 5.9 (bd, 1H), 5.4 (bt, 1H) 4.7 (bt, 1H), 2.8 (m, 1H), 2.0 (s, 3H), 1.6 (m, 1H), 0.9 (s, 9H), 0.1 (s, 6H). ¹³C NMR (CDCl₃): 170.8, 138.8, 131.1, 76.9, 74.8, 41.1, 25.8, 21.1, 18.1, -4.6 ppm. MS: m/z (M⁺) calcd 256, (M + H) obsd 257. IR (neat): C=O 1653.

Compound 18. ¹H NMR (CDCl₃): δ 6.0 (bd, 1H), 5.9 (bd, 1H) 4.7 (bt, 1H), 4.6 (bt, 1H), 2.6 (m, 1H), 1.8 (m, 1H), 0.8 (s, 9H), 0.0 (s, 6H) (-OH not visible). ¹³C NMR (CDCl₃): 136.8, 135.6, 75.1, 75.0, 44.6, 25.8, 18.1, -4.6 ppm. MS m/z (M⁺) calcd 214, (M + H) obsd 215. IR

(neat): -OH (b), 3352. Complete analytical data were compared against the control sample reported in ref 2a.

(1R,3S)-(-)-1-tert-Butyldimethylsilyloxycyclopentan-3ol (19). A 5-gal autoclave was charged with nickel(II) acetate tetrahydrate (136 g, 0.546 mol) and ethanol (6.6 L). The mixture was stirred at room temperature while a 1 M solution of NaBH₄ in ethanol (550 mL) was added in one portion. A solution of 18 (2.19 kg, 10.23 mol) in ethanol (2.2 L) was added, and stirring was stopped. The unit was purged three times with N₂, followed by three times with H₂. The autoclave was charged to 200 psi with H₂, and stirring was reinitiated. After hydrogen uptake was complete (4 h), the mixture was filtered through a prepared cake of filter aid (500 g) and charcoal (35 g) and washed with ethanol (4 L). The filtrate was evaporated at 40 °C/50 Torr to give 2.098 kg of (1R,3S)-(-)-1-tert-butyldimethylsilyloxycyclopentan-3-ol (19, 95% yield, 92% pure by GC) (Column, CDX- β 10 m × 0.25 mm × 0.25 μ m, T = 100 °C, $t_{\rm R}$ of 19 = 9.89 min). ¹H NMR (CDCl₃): δ 4.4 (bt, 1H), 4.3 (bt, 1H), 3.0 (bs, 1H, -OH), 1.5-2.0 (m, 6H), 0.8 (s, 9H), 0.0 (s, 6H).

9N-[(1'R,3'R)-trans-3'-tert-Butyldimethylsilyloxycyclopentanyl]adenine (20). A solution of 19 (1.73 kg, 8.00 mol), TBME (14 L), and Et₃N were combined and cooled to -5 °C. MsCl (744 mL, 9.6 mol) was added at such a rate that the reaction temperature did not exceed 15 °C (total addition time was 2 h). The reaction was monitored by GC (injector temperature, 190 °C; detector temperature, 270 °C; program, 100 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum 10 m \times 0.53 mm \times 2.65 μ m film thickness; $t_{\rm R}$ of **19** = 2.3 min, $t_{\rm R}$ of mesylate = 5.6 min). The salts were filtered off and washed with TBME (4 L), and then the filtrate was washed with water (5 L). The organic layer was dried over MgSO₄. The drying agent was filtered off and washed with TBME (2 L), and the filtrate was concentrated at 40 °C/50 Torr to give 2.34 kg of the mesylate, which was used without further purification.

To a 10-gal reactor was charged NaH (384 g, 9.6 mol, 60% dispersion in mineral oil), DMA (12 L), and adenine 2 (1.521 kg, 11.2 mol). The solution was stirred vigorously at ambient temperature until H₂ evolution ceased. The mixture was heated to 60 °C for 2 h and then cooled to ambient temperature. The mesylate (2.34 kg, crude) was added, and the mixture was heated and maintained at 60 °C for 18 h (monitored by disappearance of mesylate on GC and formation of product by HPLC; column, ChiralPak AD 250×4.6 mm; mobile phase, 85% pentane/15% IPA; flow rate, 1 mL/min; $t_{\rm R}$ of **20** = 10.2 min). The reaction mixture was cooled to room temperature and quenched with water (24 L). The mixture was extracted with ethyl acetate/toluene $(3:1, 2 \times 20 \text{ L})$, and the organic layers were combined and washed with water (30 L) (NaCl may be added to help the resulting emulsion disperse). The organic layer was separated and dried over MgSO₄ (2 kg). The drying agent was filtered off and washed with ethyl acetate (2 L), and the filtrate was concentrated at 50 °C/50 Torr to produce 2.24 kg of crude 20. The oily residue was dissolved in hot methanol (4 L), and the solution was allowed to stand at ambient temperature for 24 h. The crystals which formed were filtered off and washed with heptane (2 L) to give 902 g of 9N-[(1'R,3'R)-trans-3'-tert-butyldimethylsilyloxycyclopentanyl]adenine (**20**) in 34% yield. Complete analytical data were compared against the control sample reported in ref 5a.

9N-[(1'R,3'R)-trans-3'-Hydroxycyclopentanyl]adenine Hydrochloride (1). 20 (2.73 kg, 8.20 mol) was dissolved into 15 L of warm ethanol and polish-filtered into a 30-gal reaction vessel. The mixture was cooled to room temperature, and to this was added 2.7 L of 6 N HCl in ethanol over a period of 1 min. The reaction mixture was stirred for 14 min, and then 16 L of 1:1 heptane/ethanol was added. The reaction mixture was cooled to and maintained at 0 °C for 17 h. The white precipitate was filtered off via centrifuge and washed with 8 L of heptane. The white solid was allowed to air-dry for 5 h and then placed in a humidity chamber overnight. This gave 1.98 kg of the stable monohydrate of 9N-[(1'R,3'R)]-trans-3'-hydroxycyclopentanyl]adenine hydrochloride (1, MDL 201449A, 94% yield, 96.8% pure) (HPLC: column, ChiralPak AD 250×4.6 mm; mobile phase, 20% pentane/80% MeOH; flow rate, 1 mL/min; t_R of MDL 201449A = 22 min). IR (KBr, cm^{-1}): 3500-3000,1690. MS: m/z (M⁺) calcd 219.62, obsd 219. Mp (uncorrected) = 245 °C. Anal. Calcd for $C_{10}H_{14}N_5O$: C, 43.88; H, 5.89; N, 25.59. Found: C, 44.14; H, 5.78; N, 25.65. Complete analytical data were compared against the control sample reported in ref 5a.

(1R)-(-)-10-Camphorsulfonic Acid (CSA) Salt Purification Procedure of 9N-[(1'R,3'R)-trans-3'-tert-Butyldimethylsilyloxycyclopentanyl]adenine (20). 20 (4.78 g. 0.014 mol) was dissolved in ethyl acetate (75 mL). (1R)-(-)-10-Camphorsulfonic acid (3.0 g, 0.013 mol) was added, and the mixture was stirred vigorously for 18 h. The solid was filtered off to give 5.79 g of the salt that was 98.17% pure by HPLC (column, ChiralPak AD 250×4.6 mm; mobile phase, 85% pentane/15% IPA; flow rate, 1 mL/min; $t_{\rm R}$ of **20** = 10.2 min). This was dissolved into CH₂Cl₂ (150 mL) and washed with 2×100 mL of 1 N NaOH and then 100 mL of water, and the organic layer was dried over MgSO₄. The drying agent was filtered off and washed with 40 mL of CH₂Cl₂, and the filtrate was removed at 30 °C/50 Torr to give 3.25 g of 9N-[(1'R,3'R)-trans-3'-tert-buty]dimethylsilyloxycyclopentanyl]adenine (20, (71% yield) that was 98.3% pure by HPLC.

(1*R*,4*S*)-(-)-4-Acetoxy-2-cyclopentenol (6). A total of 115.4 g (0.45 mol) of 17, 500 mL (0.50 mol) of TBAF (1.0 M in THF), and 7 mL (0.05 mol) of Et₃N were charged to a 1-L three-necked flask equipped with stirrer and continuous nitrogen purge. The reaction was monitored by TLC (30% ethyl acetate/70% heptane; R_f of 17 = 0.5, R_f of 6 = 0.1; the average reaction time was 30 min.) The reaction mixture was evaporated onto silica gel (500 g) at 25 °C/50 Torr. The material was loaded onto a column of 1 kg of silica gel and eluted with 3:7 ethyl acetate/hexane. The fractions containing product were combined and concentrated at 35 °C/50 Torr to give a brown oil. The product was crystallized from

250 mL of TBME and 250 mL of hexane at 0 °C for 24 h. The crystals which formed were filtered off and washed with 1:1 TBME/hexane. The solid was air-dried to give 32 g (50%) of (1R,4S)-(-)-4-acetoxy-2-cyclopentenol (6). Complete analytical data were compared against the control sample reported in ref 1b.

(1*R*,3*S*)-(-)-1-acetoxycyclopentan-3-ol (7). A mixture of 11.2 g (45 mmol) of nickel acetate tetrahydrate, 42 mL (42 mmol) of 1 M NaBH₄ in ethanol, 167.3 g (1.18 mol) of **6**, and 2.2 L of ethanol was charged to a 2-gal autoclave. The reaction mixture was subjected to 100 psi H₂ for 4 h. After H₂ uptake had ceased, the catalyst was filtered off on a pad of Celite and charcoal. A total of 2 mL of Et₃N was added to the filtrate, and the solvent was removed at 50 °C/ 50 Torr to give 147 g (87%) of (1*R*,3*S*)-(-)-1-acetoxycyclopentan-3-ol (7). Complete analytical data were compared against the control sample reported in ref 1b.

9N-[(1'R,3'R)-trans-3'-Acetoxycyclopentanyl]adenine (9). A mixture of 180 g (1.25 mol) of **7**, 209.1 mL (1.5 mol) of Et₃N, and 1.5 L of TBME was charged to a 3-L three-necked flask equipped with stirrer, thermometer, and continuous nitrogen purge. The reaction mixture was cooled to -10 °C, and 107 mL (1.38 mol) of MsCl was added at such a rate that the reaction temperature did not exceed 10 °C. The reaction was complete after 1 h (TLC: 10:90 ethyl acetate/ heptane; R_f of **7** = 0.0, R_f of mesylate = 0.70). The reaction mixture was filtered, the filter cake was washed with 1 L of TBME, and the filtrate was concentrated at 30 °C/50 Torr to give 222.3 g of the mesylate.

A total of 202.7 g (1.5 mol) of adenine 2, 60 g (1.5 mol) of NaH, and 1.5 L of DMA was charged to a 3-L threenecked flask equipped with stirrer, thermometer, condenser, and continuous nitrogen purge. The mixture was heated to 70 °C for 1 h and then cooled to 50 °C. A total of 222.3 g of mesylate was added to the reaction mixture. The resulting slurry was heated to and maintained at 70 °C for 4 h and then cooled to room temperature and stirred for 18 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated at 50 °C/50 Torr to give the crude product. The product was purified by column chromatography (1 kg silica gel column and eluting with 3:7 hexane/ethyl acetate). The fractions containing product were combined and concentrated at 35 °C/50 Torr to give 180 g of crude product, which was recrystallized two times from MEK (2 L/150 g). The solid was filtered off, washed with MEK, and air-dried to give 120 g (36%) of 9N-[(1'R,3'R)-trans-3'-acetoxy-cyclopentanyl]adenine (9). Complete analytical data were compared against the control sample reported in ref 1b.

9N-[(1'R,3'R)-trans-3'-Hydroxycyclopentanyl]adenine Hydrochloride (1). A total of 120 g (0.46 mol) of 9, 700 mL of EtOH, and 25 mL of H₂O was charged to a 3-L three-necked flask equipped with stirrer, thermometer, condenser, and continuous nitrogen purge. A total of 90 mL of 6 N HCl in ethanol was added to the reaction mixture, which was heated at 70 °C for 23 h. The reaction mixture was cooled, and 1 L of 2:1 heptane/ethanol was added. The mixture was stored at 0 °C for 24 h. The solid which crystallized was filtered off, washed with 1 L of heptane, and dried at 35 °C/100 Torr for 6 h. The product was hydrated in a humid oven for 18 h to give 107 g (85%) of 9N-[(1'R,3'R)-trans-3'-hydroxycyclopentanyl]adenine hydrochloride, (1), with 99.5% purity (HPLC: column, ChiralPak AD 250×4.6 mm; mobile phase, 20% pentane/80% MeOH; flow rate, 1 mL/min; t_R of MDL 201449A = 22 min). Anal. Calcd for C₁₀H₁₅NO₂·HCl (MW 273.72): C, 43.88; H, 5.89; N, 25.59. Found: C, 44.18; H, 5.86; N, 25.53. Complete analytical data were compared against the control sample reported in ref 5a.

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