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ARTICLE

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Multikilogram-Scale Synthesis of a Chiral Cyclopropanol and an Investigation of the Safe Use of Lithium Acetylide−Ethylene Diamine Complex

Ephraim M. Bassan,[†] Carl A. Baxter,[*,‡] Gregory L. Beutner,[*,§] Khateeta M. Emerson,[*,†] Fred J. Fleitz,[§] Simon Johnson,[‡] Stephen Keen,[‡] Mary M. Kim,[§] Jeffrey T. Kuethe,[§] William R. Leonard,[§] Peter R. Mullens,[‡] Daniel J. Muzzio,[†] Christopher Roberge,[§] and Nobuyoshi Yasuda[§]

[†]Department of Chemical Process Development and Commercialization, Merck and Co., Inc., Rahway, New Jersey 07065, United States

[‡]Global Process Chemistry, Merck, Sharp and Dohme Ltd., Hertford Road, Hoddesdon, EN11 9BU, U.K.

[§]Department of Process Research, Merck and Co., Inc., PO Box 2000, Rahway, New Jersey 07065, United States

Supporting Information

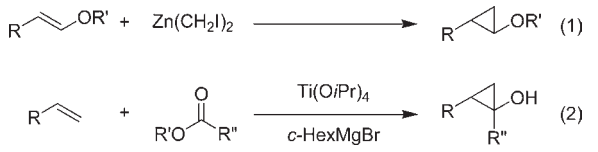
ABSTRACT: A six-step route starting from a readily available vinyl boronate was identified to produce an enantioenriched cyclopropanol in an overall 16% yield. Key steps involve the use of lithium acetylide-ethylene diamine complex **5** and an enzymatic resolution of a racemic cyclopropanol acetate. Process safety considerations surrounding the use of **5** were examined, and an improved procedure is described which was safely demonstrated at multikilogram scale.

INTRODUCTION

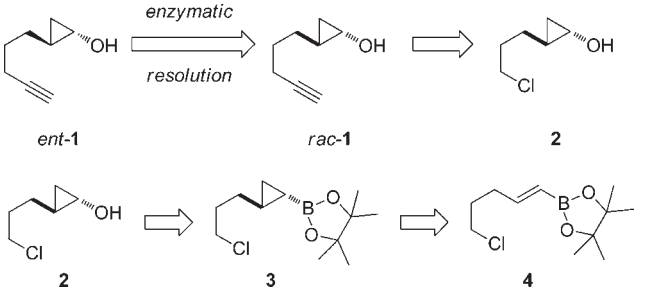
Despite recent advances in asymmetric Simmons−Smith[1] and transition metal-catalyzed cyclopropanations,[2] the preparation of chiral, nonracemic cyclopropanols remains a formidable challenge.[3] The two most common routes to cyclopropanols are the Simmons−Smith cyclopropanation of vinyl ethers (Scheme 1, eq 1) and the Kulinkovich cyclopropanation[4] (Scheme 1, eq 2). These reactions have both been investigated with chiral catalysts and/or auxiliaries, although the scope and selectivity of these reactions is limited. Shi and co-workers have shown that a dipeptide-derived catalyst gives excellent yields and enantioselectivities in the Simmons−Smith cyclopropanation of ketone-derived silyl enol ethers.[5] Corey and co-workers have demonstrated that a titanium−TADDOL complex gives moderate levels of enantioselectivity in the Kulinkovich cyclopropanation of an acetate-derived ester.[6] Several auxiliary-based methods have also been developed for the Simmons−Smith cyclopropanations of chiral vinyl ethers[7] and chiral boronate esters,[8] but these methods typically suffer from low yields and difficulties in the removal of the chiral auxiliary. Additionally, the asymmetric synthesis of cyclopropyl boronates has been realized starting from allylic carbonates[9] or cyclopropenes,[10] but both procedures possess significant limitations in terms of scope.

Considering the state of the art for the asymmetric synthesis of cyclopropanols, the development of a scalable synthesis of *ent*-**1** to support an ongoing drug discovery program presented a significant challenge (Scheme 2). Since the asymmetric Simmons−Smith cyclopropantion of silyl enol ethers has only been demonstrated with ketone-derived substrates and there is little precedent for the Kulinkovich cyclopropanation of formate esters, the literature provided few options in terms of developing a catalytic asymmetric synthesis for *ent*-**1**. Therefore, to access the desired *ent*-**1**, an alternative six-step route starting from vinyl boronate **4** was identified which would rely on a final, enzymatic

Scheme 1. Cyclopropanol synthetic methods



Scheme 2. Retrosynthetic analysis of *ent*-1



resolution to generate the desired, enantioenriched cyclopropanol. The racemic alkynyl cyclopropanol *rac*-**1** could be generated from the corresponding cyclopropanol chloride **2**. The cyclopropanol would be unmasked via cleavage of boronate **3** which would be prepared from the *E*-vinyl boronate **4**, a commercially available compound.

Even after successful demonstration of this new route at laboratory scale, significant issues remained, particularly in the context of the safe use of lithium acetylide−ethylene diamine

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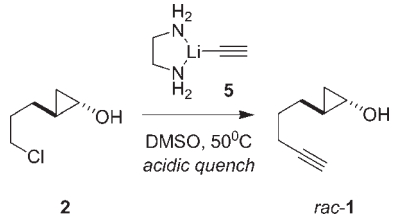
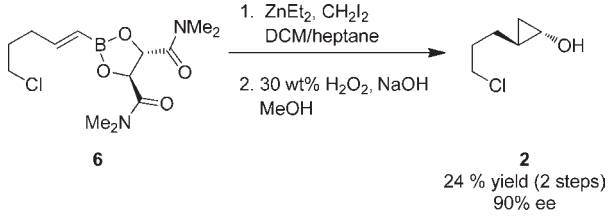
Scheme 3. Alkynylation of 2 with lithium acetylide−ethylene diamine complex 5



Scheme 4. Diastereoselective cyclopropanation of 6



complex **5** for installation of the terminal alkyne on larger scale (Scheme 3). In this report, we describe the development and successful implementation of a synthesis of *ent*-**1** on a multikilogram scale. Detailed studies focusing on the hazards of the key alkynylation step with **5** are described which shed light on the hazards of this commercially available reagent and defined a clear path forward for its safe use.

RESULTS AND DISCUSSION

Development of a Synthesis of the Alkynyl Cyclopropanol *rac*-1. The cyclopropanation of vinyl boronates has been reported in the literature, predominantly in the context of diastereoselective Simmons−Smith cyclopropanations.[8] Initial attempts to perform a diastereoselective cyclopropanation of a tartaramide-modified vinyl boronate **6**[8i] gave a 24% yield of **2** after oxidative cleavage, with significant process impurities which could only be removed after a difficult chromatography (Scheme 4).

Therefore, the racemic cyclopropanation of the commercially available pinacol vinyl boronate **4**[11] was investigated. Literature precedent existed for this transformation, but only moderate yield was obtained after running the reaction for 10 h at 50 °C.[8h] In our hands, treatment of **4** with bis-iodomethylzinc ($Zn(CH_2I)_2$) prepared from diethylzinc and diiodomethane gave poor conversion (<5%), even after prolonged reaction times at room temperature. The electron-deficient nature of this alkene combined with the lack of a coordinating group was suspected as the cause of this poor reactivity.[12] Therefore, the use of the trifluoroacetic acid-modified reagent developed by Shi and co-workers[13] was attempted, and it showed a dramatic increase in reactivity at room temperature. After formation of the iodomethylzinctrifluoroacetate ($ICH_2ZnO_2CCF_3$) from diethylzinc, trifluoroacetic acid, and diiodomethane in a dichloromethane (DCM)/hexane mixture at 0 °C, addition of vinyl boronate **4** followed by stirring at room temperature for 16 h gave >98% conversion to the cyclopropyl boronate **3** in 79% isolated yield after only an acidic aqueous workup (Scheme 5). The high conversion and clean impurity profile obtained under the Shi conditions represented a significant improvement when compared to results using $Zn(CH_2I)_2$.

With **3** in hand, investigation of the oxidation of the boron−carbon bond was undertaken. Initial attempts to employ sodium perborate[8h,14] led to significant decomposition. However, it was found that treatment of **3** with 1 equiv of 10 M sodium hydroxide in methanol at 0 °C followed by 2.0 equiv of 30 wt % hydrogen peroxide gave clean conversion to **2** after an aqueous workup. Initial attempts showed that extractive removal of pinacol was challenging and would require further development for large scale (vide infra); thus, the removal of pinacol from crude **2** was accomplished at this stage of development by column chromatography to give a 69% yield of the desired chloro cyclopropanol **2**.

At this point, the direct displacement of the primary chloride in **2** to generate the terminal alkyne in **1** was investigated. This would avoid the installation of an oxygen-protecting group and the addition of two steps to the synthesis for protection and deprotection of this early-stage intermediate. The lithium acetylide−ethylene diamine complex **5** seemed an attractive choice for an alkynylating agent since it is a relatively air-stable, commercially available solid. A survey of the literature on alkynylations with **5** revealed that this reaction was known to proceed even in the presence of protic functionality such as a carboxylic acid.[15] However, a more pressing issue was the fact that alkyl chlorides showed poor reactivity with **5**. Extensive literature examples exist on the displacement of bromides,[16] iodides,[17] and oxygen-centered leaving groups such as tosylates, triflates, and epoxides[18] with **5**, but only a single publication could be found on the reaction of alkyl chlorides.[19] A highly polar solvent such as dimethyl sulfoxide (DMSO) was required for the displacement reaction. Investigations on the reaction of **2** with **5** revealed that the only viable solvents for this transformation were *N*,*N*′-dimethylacetamide (DMAc), *N*-methylpyrrolidinone (NMP), and DMSO. DMAc gave good conversion, but the impurity profile was not as favorable as the reaction performed in either DMSO or NMP. Although the impurities formed during reactions in DMAc were not identified, the possibility of acetylation of either **5** or **1** by DMAc could not be ruled out.

The initially developed conditions called for the use of 2.1 equiv of **5** in DMSO (Scheme 6). Due to the low reactivity of the chloride, long reaction times were required at room temperature to obtain >90% conversion. However at 50 °C, after only 1 h, >98% conversion and a 76% yield of *rac*-**1** could be obtained. The crude solution was directly acetylated to give cyclopropyl acetate, *rac*-**7**, which could be used directly in the subsequent enzymatic resolution.

Although the alkynylation of the unprotected cyclopropanol **2** did avoid the need for a protecting group strategy, the use of excess lithium acetylide−ethylene diamine complex **5** to perform both the deprotonation of the cyclopropanol and the alkynylation led to the generation of a full equivalent of acetylene. The uncontrolled release of acetylene gas would pose a significant risk upon scale-up. Furthermore, the known incompatibility of DMSO and strongly basic reagents raised additional safety concerns which would require careful investigation prior to implementing this procedure on larger scale.[20]

An examination of the stability of lithium acetylide−ethylene diamine complex **5** in DMSO immediately confirmed the concerns about processing the reaction on large scale. Testing was carried out using a closed system accelerating rate calorimeter (ARC) corrected for thermal inertia such that the test results

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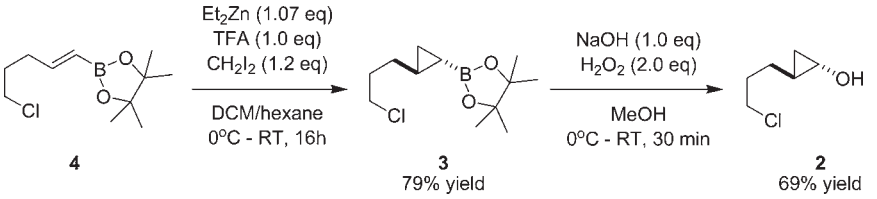
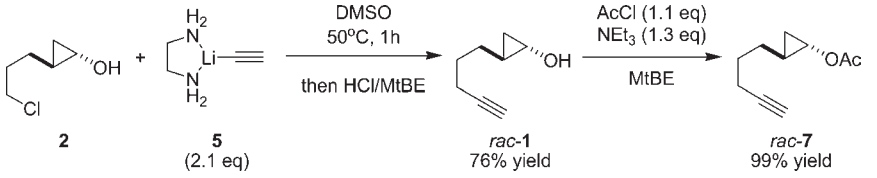
Scheme 5. Preparation of chloro cyclopropanol 2



Scheme 6. Alkynylation of the chloro cyclopropanol 2 with 5



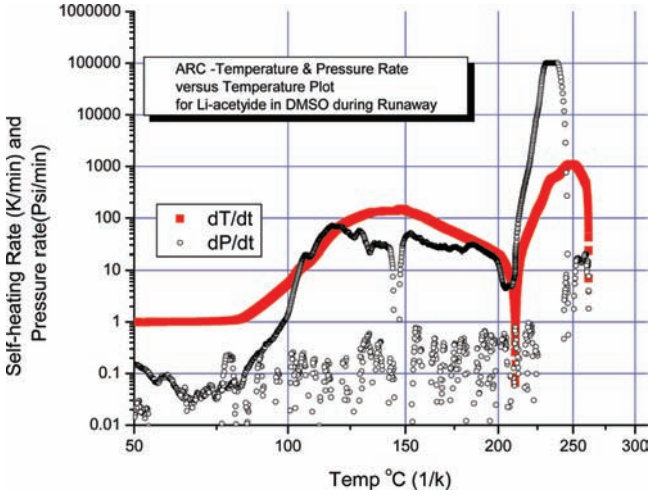


Figure 1. Rates of self-heating and pressure generation vs temperature for **5** in DMSO.

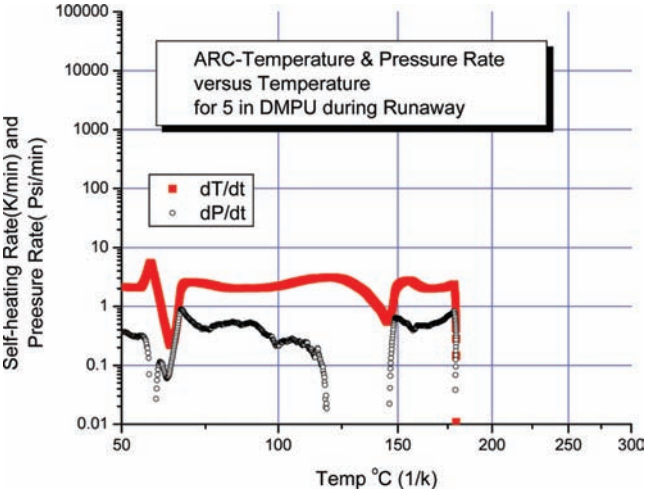


Figure 2. Rates of self-heating and pressure generation vs temperature for **5** in DMPU.

mimic what can be expected in the factory (500-L vessel or larger). The test results demonstrated that **5** in DMSO was unstable at temperatures greater than 50 °C, which could potentially lead to thermal runaway (Figure 1). The ARC results showed that around 50 °C a very slow adiabatic runaway reaction started which accelerated to a rapid but controllable rate. A large amount of heat was generated. The approximate adiabatic temperature rise observed was +170 K. This activity self-heated the sample to 210 °C where a second decomposition reaction involving the DMSO solvent occurred, resulting in an extremely violent and uncontrollable runaway reaction. Test results showed that the temperature rose at a rate exceeding 1000 K/min, and an associated pressure generation rate exceeded 100,000 psi/min. Over 4000 psi was generated, causing the test equipment to fail. At this point it was obvious that the process was not safe to scale up.

Since initial studies indicated that a polar aprotic solvent would be required for high conversions to *rac*-**1** and DMSO was clearly not suitable for further development, a brief screen of other polar aprotic solvents was undertaken to identify an alternative (Table 1, Route A). Using 2.1 equiv of lithium acetylide−ethylene diamine complex **5**, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidone (DMPU), DMAc and NMP were identified as potential candidates on the basis of the high conversions observed at room temperature. Examination of the stability of **5** in DMPU using the ARC revealed that **5** in DMPU started to slowly decompose at 70 °C. However, the resulting adiabatic temperature rise was about half of that observed in DMSO, and the maximum rate of temperature increase was reduced by at least an order of magnitude (Figure 2). More importantly, the violent higher-temperature secondary decomposition was not encountered. ARC testing using **5** in NMP gave results comparable to those observed with DMSO for the controllable first exotherm. However, even at temperatures above 215 °C, no secondary decomposition was observed. From this initial data, the thermal stability of **5** in both DMPU and NMP suggested that either would be a safe solvent for scale-up of the reaction of **2** with **5** at 50 °C. However, from a safety perspective, DMPU was clearly the better choice.

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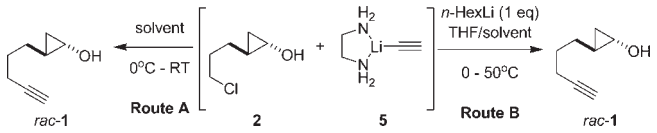
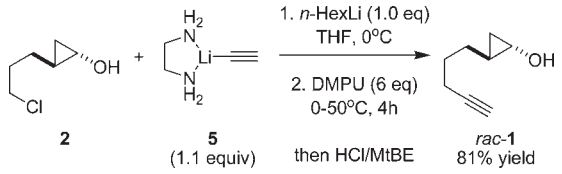
Table 1. Survey of solvents for reactions of 2 with 5



	route A: 2.2 equiv **5**		route B: 1.1 equiv **5**, 1 equiv *n*-HexLi	
	1 h, RT (% conv)	20 h, RT (% conv)	conv, time (%, h)	yield (%)
DMSO	90	>98	–	–
DMAc	10	>98	58, 4	24
NMP	23	>98	98, 2.5	56
DMPU	>98	ND	96, 4	81

Scheme 7. Optimized conditions for formation of *rac*-1



Having addressed the issue of reaction solvent, our attention turned to the issue of acetylene generation during the reaction. In the original procedure, 2.1 equiv of **5** were employed to both deprotonate the cyclopropanol and perform the displacement of the chloride to give *rac*-**1**. We hoped to identify a sacrificial base to replace the extra equivalent of **5** used in the original procedure and thus avoid the generation of a full equivalent of acetylene during the reaction. Treatment of a solution of **2** in tetrahydrofuran (THF) at 0 °C with 1 equiv of *n*-hexyllithium to form the corresponding alkoxide, followed by transfer of that solution into a suspension of **5** in DMPU before heating to 50 °C, proved successful (Table 1, Route B). On the basis of yield, the use of DMPU was clearly superior to NMP or DMAc. Using DMPU as the solvent, an 81% isolated yield could be obtained after acidic workup as described above (Scheme 7). The final solvent composition of the reaction was approximately 1:1 THF/DMPU, and it was hoped that the amount of DMPU could be reduced to increase volume efficiency and decrease the use of this costly solvent. However, increasing the ratio of THF to DMPU led to low conversions, even after prolonged reaction times.

Despite the use of a sacrificial base to minimize acetylene gas evolution, the potential to form acetylene gas in the headspace from the decomposition of **5** was a major concern and needed to be investigated. Acetylene is very sensitive to excess pressure, excess temperature, static electricity, and/or mechanical shock. Acetylene is incompatible with certain materials and metals, such as copper.[21] It is extremely flammable and readily forms explosive mixtures with air over an unusually broad range of concentration.[22] The explosive limits can range from 2.5 to 81% in air.[23] Acetylene will violently self-react at >15 psi.[24] The high bond energy of the carbon−carbon triple bond makes acetylene explosions more violent than those of most other fuels. For these reasons, the electrical classification of acetylene in the United States is Class 1, Group A.[25] Acetylene is categorized by itself in Group A due to the unique hazards of this compound. As a point of reference, Group B includes hydrogen and, in some situations, ethylene oxide and butadiene. Due to the special safety controls required for the use of acetylene gas, few if any US pharmaceutical pilot plants are rated for Class 1, Group A. In the EU, however, acetylene has an electrical classification of group IIC, which also includes hydrogen, and some European pharmaceutical pilot plants are rated for group IIC. Although monitoring of the release of acetylene gas during this reaction is required in all cases, the quantification of acetylene in the headspace would have implications regarding where this chemistry could be performed on kilogram scale.

In order to understand and quantify the timing and the amount of acetylene produced during this reaction, a ReactIR 4000 was used to measure the evolution of acetylene gas (absorption at 3300 cm^{-1}) in the headspace. The ReactIR 4000 was equipped with an online gas cell connected to a 250-mL jacketed flask (see Experimental Section for details). The gas phase in the reactor was examined over the entire course of the reaction by purging dry nitrogen gas through the headspace at a rate of 20 mL/min. A condenser at 5 °C was used to minimize the loss of THF. To quantify the exact amount of acetylene present, calibration with a known mixture of acetylene in nitrogen was used to create a calibration curve.

When the optimized procedure using a sacrificial base and 1.1 equiv of **5** (Scheme 7) was performed in the apparatus equipped with the ReactIR, it was observed that acetylene was still evolved during the reaction (Figure 3), with the majority of the acetylene evolving during the early stages of the reaction. It was found that suspending **5** in dry DMPU led to some acetylene release (<1% acetylene in the headspace). During the reaction, the bulk of the acetylene was released upon addition of the solution of the lithium alkoxide of **2** in THF to the suspension of **5** in DMPU and the subsequent heating to 50 °C. At its highest point, the level of acetylene measured in the headspace during the reaction was 7.2% (Figure 3). The acetylene level reached this point at t = 50 min and then slowly dropped over the remainder of the reaction. Monitoring was continued during the quench of the reaction with 1 M HCl, but no acetylene release was evident at this point. On the basis of these results, it was clear that even with a sacrificial base present, some acetylene was being produced. Therefore, safely performing this chemistry on kilogram scale in countries that use the American electrical classification system would require a pilot plant rated for Class 1 Group A gases, and in countries that use the European system would require a pilot plant capable of handling class IIC gases. If the reactor and/or its venting pathways are not rated for acetylene, the amount of acetylene in the headspace should be limited to ≤1% for single batch and

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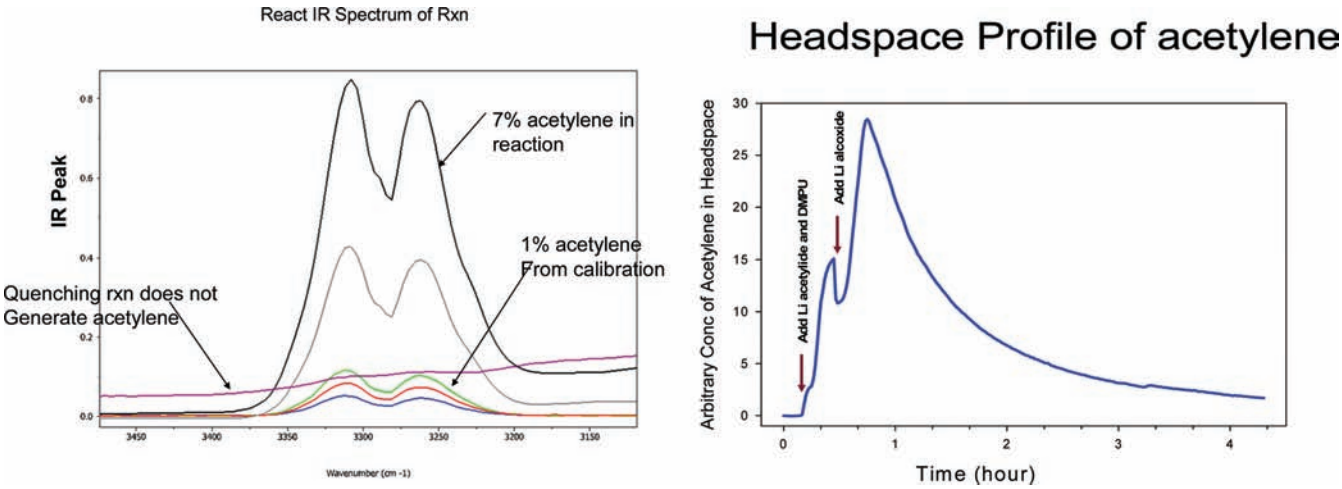


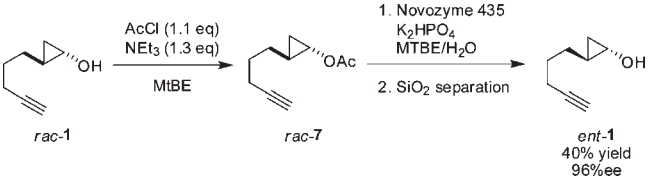
Figure 3. ReactIR analysis of reactor headspace for acetylene.

≤0.6% for regular production, placing significant restrictions on the broad utility of this chemistry at plant scale. Despite the low levels of acetylene which can potentially be produced by this reaction, care should be taken when using **5** on any scale to avoid potentially dangerous explosions from the buildup of acetylene.

Having examined the safety concerns surrounding lithium acetylide—ethylene diamine complex **5** and gained a better understanding of the alkynylation of **2**, we had some confidence about continuing the development of this route at larger scale. Therefore, with a route to the racemic cyclopropyl acetate *rac*-**7** in hand, investigations of the crucial enzymatic resolution step were undertaken (Scheme 8). Hydrolysis of the cyclopropyl acetate *rac*-**7** was screened against our library of commercially available lipases and amidases, consisting of a number of lyophilized powders, liquid enzyme preparations, and immobilized enzyme preparations. For the lyophilized powders and liquid enzyme preparations the screening was conducted using a 0.1 M, pH = 8.0, aqueous phosphate buffer in a 96-well plate format. The cyclopropyl acetate was dispensed to each reaction tube as a solution in DMSO to give a substrate concentration of 5 mg/mL and a DMSO concentration of 10 vol %. For the immobilized enzyme screen, MTBE was shaken in a separatory funnel with a solution of 0.1 M, pH = 8.0, aqueous phosphate buffer, and then the layers were allowed to separate. The cyclopropyl acetate was then added to a portion of the buffer-saturated MTBE to give a substrate concentration of 5 mg/mL. The substrate/MTBE solution was then mixed with a previously dispensed quantity of the immobilized enzymes in a 96-well plate format at 30 °C. The reactions were then monitored for conversion and enantiomeric excess (see Experimental Section for GC conditions).

From the initial screening results, Novozym 435 with MTBE as solvent was selected for further reaction optimization. It was identified that the desired enantiomer *ent*-**1** was the hydrolyzed product of the reaction with *rac*-**7**. Screening of additional organic solvents (ethyl acetate, heptane, toluene, THF, acetonitrile, etc.) for an increase in hydrolysis selectivity did not offer any advantages over the initial MTBE conditions. With the MTBE solvent system, no significant background hydrolysis of *rac*-**7** to *rac*-**1** occurred when the MTBE solution was shaken with a 0.1 M aqueous solution of potassium phosphate dibasic (approximate pH of 8.6), indicating that there would be no unselective, uncatalyzed background hydrolysis of this species under these

Scheme 8. Enzymatic resolution of *rac*-7



conditions. Using these more basic conditions removed a pH adjustment from the original procedure and modestly simplified the reaction setup. Finally, the charges of cyclopropyl acetate *rac*-**7** and Novozym 435 were optimized to give a reaction rate that was sufficient to complete the reaction in one day but was still slow enough that overhydrolysis (and a corresponding loss in product enantiomeric excess) could be avoided. When the desired end point of the reaction was obtained (product ee of 96%, approx 40% conversion) the reaction mixture was filtered to remove the enzymatic catalyst and halt any further hydrolysis. The crude reaction mixture was concentrated and then solvent switched to heptane for the subsequent chromatographic purification. Since all of the reactions thus far were to be conducted as a through-process with no isolations or purification, separation of the mixture of *ent*-**1** and *rac*-**7** would serve not only to give the enantioenriched product but also to remove process impurities generated thus far. Purification by column chromatography was successful at removing a variety of impurities which had been formed during this five-step through-process and gave material of sufficient quality for the final delivery.

■ LARGE-SCALE DEMONSTRATION OF THE SYNTHESIS OF CYCLOPROPYL ALCOHOL *RAC*-1

Having established proof of concept for the synthesis of *ent*-**1** as well as identified the relevant issues for the safe handling and use of lithium acetylide—ethylene diamine complex **5**, the procedure was ready for scale-up to multikilogram scale. Although vinyl boronate **4** is commercially available, due to cost and lead-time it was decided to implement a quick synthesis from the chloroalkyne **8** (Scheme 9). The hydroboration of **8** was carried out using pinacol borane in the presence of a catalytic amount of BH_3—THF (0.05 equiv) and cyclohexene (0.1 equiv).[26]

The key concerns with this step were the highly exothermic charges of the reagents to an essentially neat reaction mixture.

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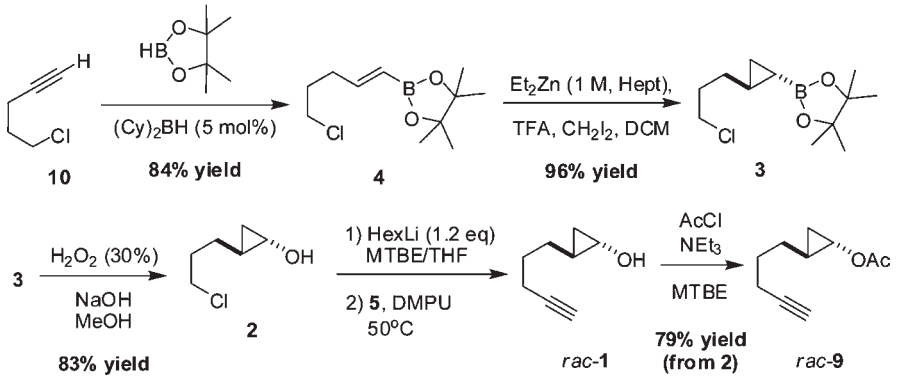
Scheme 9. Large-scale demonstration of the synthesis of *rac*-7



The addition of cyclohexene to borane and the subsequent addition of the alkyne **8** to this mixture were highly exothermic, but these could be controlled by adjusting addition rate. A RC-1 (reaction calorimeter) run on the final pinacol borane addition at 30 °C over 2 h showed a 40% accumulation of reagents with a reaction exotherm of 154 kJ/mol and an adiabatic temperature rise of >300 K. Thus, it was decided to do an extended addition over at least 2 h, with careful monitoring of the exotherm throughout the charge. On a 20-kg scale the pinacol borane addition took 4 h 40 min, and after a further 50-min age, the batch temperature stabilized, and ^{1}H NMR showed 85% conversion. After an overnight age, 94% conversion[27] was achieved, and the batch was then quenched and worked up to afford 38 kg of **4** in 84% yield.

The Simmons−Smith reaction of **4** (80 wt % solution in heptane) was efficient on 20-g runs, achieving >98% conversion after an overnight age. The reactions were very clean, giving **3**, after workup and concentration, as a solution in heptane in >90% yield (>95% purity by ^{1}H NMR and GC). Large exotherms were observed upon sequential addition of the reagents; therefore, the reaction was examined further using DSC (differential scanning calorimeter) and RC-1 calorimetry. DSC showed no exotherms in the slurries after additions, quench, and concentration. RC-1 was used for the reagent additions to examine the heat transfer of the reaction in order to calculate a safe addition rate and vessel jacket temperature in the plant. For the specific vessel used in the pilot plant, these data showed the following:

(1) Addition rates and vessel jacket temperatures needed to maintain a reaction at 3 °C were:
TFA addition to Et_2Zn: 32.6 KJ/mol exotherm with adiabatic temperature rise of ∼57 K. TFA addition could be done over 80 min with jacket at −11 °C.
CH_2I_2 addition to TFA/Et_2Zn/DCM slurry: 9.3 KJ/mol exotherm with adiabatic temperature rise of ∼12 K. CH_2I_2 addition could be done over 20 min with jacket at −10 °C.
Substrate addition: 23.6 KJ/mol exotherm with adiabatic temperature rise of ∼28 K. Substrate addition could be done over 45 min with jacket at −12 °C.

(2) Addition rate and vessel jacket temperature to maintain the quench at 25 °C were:
Quench with aqueous HCl: 7.4 kJ/mol exotherm with adiabatic temperature rise of ∼8 K. On scale addition could be done over 10 min with jacket at +6 °C.

On scale the Simmons−Smith reaction was run in two batches using 34.3 kg of **4**. Both proceeded identically (>98% conversion) and gave **3** as a solution in heptane (44.8 kg at 78 wt %, 96% yield).

For the oxidation of the boronate to the cyclopropyl alcohol, this was achieved by treating boronate **3** with 10 M sodium hydroxide (1.0 equiv) and aqueous hydrogen peroxide (30%, 1.2 equiv). Once the oxidation was complete, the reaction was quenched with hydrochloric acid followed by aqueous sodium sulfite and stirring overnight to ensure complete hydrolysis of any intermediate boronate species. Although all four of the additions are exothermic, running this chemistry in the RC-1 confirmed that there was very little heat accumulation at the end of each of these additions, indicating that the exotherms observed could be controlled by adjusting the addition rate, and that reasonable addition times would be achievable on scale. Furthermore, GC analysis both part way through and at the completion of the peroxide addition indicated that the reaction was almost instantaneous at −5 to 5 °C.

In previous lab runs the alcohol **2** was isolated by extraction into MTBE and purification by column chromatography to remove pinacol. It was found, however, that the chromatographic removal of pinacol could be avoided by washing the MTBE extracts with water several times. DCM or toluene could be used in place of MTBE, but its relative ease of removal and disposal made it a better choice for scale-up. Therefore, the quenched reaction mixture was extracted twice with MTBE, and the combined extracts were then washed once with 0.5 M sodium hydroxide and then washed three times with water. The resulting MTBE solution was azeotropically dried by distillation and then concentrated to minimum volume to afford a 75% corrected yield of alcohol **2**. The final material typically contained less than 2% pinacol relative to **2** (based on GC) and, excluding solvents, contained only one impurity larger than this (3% LC area percent (LCAP)). A total of 8% of desired product **2** was lost to the initial aqueous layer and the four washes. It was decided to use crude **2** directly in the next step. This process was successfully run on 35 kg scale, without incident, to afford a 27 wt % MTBE solution of alcohol **2**, containing 16.1 kg of desired product (83% yield). Pinacol level, aqueous losses, and purity profile all matched typical lab runs.

The Li-acetylide/DMPU chemistry developed to avoid the generation of acetylene was scaled. In order to achieve optimum conversion and purity during the course of the reaction when using the bulk stream of **2**, the conditions were altered slightly. Upon changing the reaction parameters, we found the most successful and consistent procedure was deprotonation of the alcohol in MTBE and THF at <−10 °C with 1.2 equiv HexLi, followed by addition of this alkoxide to the lithium acetylide−ethylene diamine complex **5** in DPMU at <25 °C and heating to 50 °C. This slightly modified procedure resulted in good conversions, while keeping the impurities at less than 5 GC area percent

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(GCAP) each. Using 16.1 kg of **2**, the alkynyl alcohol *rac*-**1** was isolated as a 31 wt % solution, which was used directly in the acylation. The impurities were kept to below 3% each, with six impurities at 1−3% GCAP, and the total impurities were 13 GCAP.

The acylation of cyclopropanol *rac*-**1** to give cyclopropyl acetate *rac*-**7** proceeded without incident using Et_3N (1.3 equiv) and AcCl (1.2 equiv). The resulting MTBE solution of cyclopropyl acetate *rac*-**7** contained 12.5 kg by assay (46 wt %; 79% yield over two steps from alcohol **2**) and was ready for use in the enzymatic hydrolysis.

Completion of the preparation of *ent*-**1** was performed through enzymatic hydrolysis of *rac*-**7** followed by silica gel chromatography. The crude MTBE stream of *rac*-**7** was used directly under conditions identical to those employed at smaller scales. When the reaction reached 41% conversion to *ent*-**1** with 96% ee, the reaction mixture was filtered and purified by silica gel chromatography using a EtOAc/heptanes solvent system to remove unhydrolyzed acetate *rac*-**7** and other impurities generated in the five-step through-process. Unfortunately, heating of the sample occurred upon loading onto the column, leading to some hydrolysis of the undesired acetate *rac*-**7**. Therefore, the 96% ee of *ent*-**1** obtained in the enzymatic hydrolysis of *rac*-**7** was lowered to 92% ee in the final, isolated *ent*-**1**. The undesired hydrolysis in the presence of silica was not observed on smaller scales. Despite this drawback, productivity was high and significant quantities of *ent*-**1** of acceptable quality for the downstream chemistry were produced, allowing completion of the delivery. In total, 3.48 kg of an 81 wt % solution *ent*-**1** in MTBE (2.81 kg, 30% yield from *rac*-**7**) with 92% ee was isolated. This represents an overall 15.8% yield for the six-step synthesis starting from the chloroalkyne **8**.

CONCLUSIONS

Over the course of studies towards a multikilogram synthesis of *ent*-**1**, we had the opportunity to carefully evaluate the use of lithium acetylide−ethylene diamine complex **5**. While acceptable for small-scale development, careful evaluation of the commonly employed literature conditions in DMSO revealed serious safety concerns with uncontrolled exothermic activity of mixtures of lithium acetylide−ethylene diamine complex **5** in DMSO. An interplay between chemical and thermochemical analysis of the reaction in a variety of solvents quickly led to identification of safer alternatives to DMSO. Use of either NMP or DMPU can provide a safe and practical method for the alkynylation of even unreactive chloroalkanes. Safety issues surrounding the evolution of acetylene gas during the reactions of **5** were carefully studied, and an improved process employing a sacrificial base and a stable solvent was identified and used for scaling this process. Finally, an efficient enzymatic resolution of the *trans*-cyclopropanol *rac*-**1** was developed, providing access to this deceptively complex chiral motif which could not be readily accessed through existing asymmetric methodologies. All these studies combined to allow for successful completion of the synthesis of *ent*-**1** on multikilogram scale in a safe and timely fashion to support ongoing drug discovery efforts.

EXPERIMENTAL SECTION

Preparation of 2-[2-(3-Chloro-propyl)-cyclopropyl]-4,4,5,5-tetramethyl- [1,3,2]dioxaborolane (3). To a 5-L round-bottom flask (RBF) equipped with a nitrogen inlet, mechanical stirrer, dropping funnel, and thermocouple under N_2 was added 800 mL of dichloromethane and 800 mL of a 1 M diethylzinc solution in heptane (0.8 mol, 1.07 equiv). The solution was cooled with an ice bath to an internal temperature of 3 °C. To the flask was then added from the dropping funnel a solution of 57.6 mL trifluoroacetic acid (0.748 mol, 1.0 equiv) in 200 mL of dichloromethane over 1 h, keeping the internal temperature below 10 °C. The resulting suspension was stirred for 30 min at 3 °C. To the flask was then added 72.4 mL of diiodomethane (0.897 mol, 1.2 equiv) in a single portion. After stirring at 3 °C for 30 min, 172 mL of **4** (0.748 mol, 1.0 equiv) was added to the solution in a single portion. The flask was then allowed to warm to room temperature, and a white precipitate began to form. After 3 h, GC analysis indicated the reaction was at 90% conversion. The suspension was aged for an additional 17 h or until complete consumption of **4** is observed. At that point, 800 mL of 1 M HCl (0.8 mol, 1.07 equiv) was added, and a +5 °C exotherm was observed. The biphasic mixture was stirred for 30 min to dissolve the precipitated solids, and the organic layer was separated. Extraction of the aqueous layer with 200 mL of dichloromethane, washing of the combined organic layers with 500 mL brine, and concentration in vacuo to give 194 g of **3** as a yellow oil (74 wt % in DCM, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (t, 2H, J = 6.7 Hz), 1.90 (pent, 2H, J = 7.1 Hz), 1.49 (sext, 1H, J = 7.0 Hz), 1.36 (sext, 1H, J = 7.0 Hz), 1.23 (s, 12H), 0.93 (m, 1H), 0.71 (m, 1H), 0.44 (m, 1H), −0.35 (dt, 1H, J = 9.4, 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.82, 44.74, 32.67, 32.22, 24.64, 17.22, 11.24, 0.5 (bs); GC: HP1 (30 m × 0.32 mm × 0.25 μm), 25 psi, 200 °C front inlet. Five minutes @ 50 °C, ramp 25 °C/min to 250 °C, then hold for 4 min, t_r(**4**) = 9.78 min, t_r(**3**) = 10.08 min.

Preparation of 2-(3-Chloro-propyl)-cyclopropanol (2). To a 3-L RBF equipped with a nitrogen inlet, mechanical stirrer, dropping funnel, and thermocouple was added 143 g of **3** (0.585 mol, 1.0 equiv) in 1 L of methanol. The solution was cooled with an acetone/water/dry ice bath to an internal temperature of −8 °C. To the flask was then added from the dropping funnel 58.5 mL of 10 M sodium hydroxide (0.585 mol, 1.0 equiv) over 30 min, keeping the internal temperature below 10 °C. After stirring for 30 min, 120 mL of 30 wt % hydrogen peroxide solution (1.17 mol, 2 equiv) was slowly added from the dropping funnel over 1 h, keeping the internal temperature below 10 °C. Upon completion of the addition, the cooling bath was removed, and the resulting colorless slurry was stirred at RT for 30 min or until complete consumption of **3** is observed by GC. The suspension was then cooled in an ice bath to an internal temperature 2 °C, and 375 mL 2 M HCl was added from the dropping funnel over 30 min, keeping the internal temperature below 10 °C. To this clear, yellow solution at 4 °C was then slowly added 500 mL of a 1 M solution of Na_2SO_3 from the dropping funnel, keeping the internal temperature below 10 °C. The resulting suspension was then filtered and extracted 3 × 200 mL MTBE. Concentration followed by silica gel column chromatography (6:4 hexane/ethyl acetate), to remove pinacol, gave 60.6 g of product **2** as a clear oil (90 wt %, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (t, 2H, J = 6.6 Hz), 3.27 (dt, 1H, J = 6.3, 2.6 Hz), 1.89 (pent, 2H, J = 6.8 Hz), 1.85 (bs, OH), 1.43 (sext, 1H, J = 7.0 Hz), 1.28 (sext, 1H, J = 7.0 Hz), 0.94 (m, 1H), 0.75 (m, 1H), 0.38 (q, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.21, 44.69, 31.91, 28.69, 19.69, 14.15; GC: HP1 (30 m × 0.32 mm × 0.25 μm), 25 psi, 200 °C front inlet. Five minutes @ 50 °C, ramp 25 °C/min to 250 °C, then hold for 4 min, t_r(**3**) = 10.08 min, t_r(**2**) = 7.15 min.

Preparation of 2-Pent-4-ynyl-cyclopropanol (*rac*-1). To a two-necked 500-mL round-bottom flask equipped with a temperature probe, N_2 inlet, and septum was added 27.0 g of **2** (0.201 mol,

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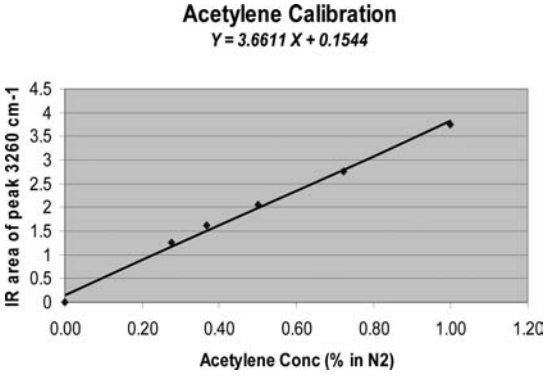
1.0 equiv, 100 g as a 27 wt % solution in MTBE) and 54 mL of THF. The solution was cooled to an internal temperature of −15 °C. To this solution was added 67.2 g of 33 wt % *n*-hexyllithium (0.241 mol, 1.2 equiv) slowly via syringe pump over 1 h, keeping the internal temperature below 0 °C. In a separate three-necked 1-L RBF equipped with a temperature probe, N_2 inlet, and septum was slurried 20.7 g of lithium acetylide−ethylenediamine complex **5** (0.221 mol, 1.1 equiv) in 136 mL of DMPU at room temperature. To this room temperature slurry was transferred via cannula over 15 min the cold solution of the deprotonated cyclopropanol. After the addition, the brown mixture was heated to an internal temperature of 52 °C for 11 h (97% conversion was observed by GC). The brown mixture was cooled with an ice bath to 3 °C, then 221 mL of 1.0 N HCl (0.221 mol, 1.1 equiv) was added slowly, keeping the internal temperature below 10 °C. The mixture was then diluted with 108 mL of MTBE and 108 mL of water before transfer to a separatory funnel and removal of the aqueous layer. The aqueous layer was extracted twice with 108 mL of MTBE, and then the combined organic layers were washed with 50 mL of water followed by 50 mL of 5% brine. The organic layer was then concentrated in vacuo to afford 31.5 g of *rac*-**1** as a yellow oil (63 wt %, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (dt, 1H, J = 2.6, 5.3 Hz), 2.25 (dt, 2H, J = 2.6, 7.6 Hz), 1.96 (t, 1H, J = 2.6 Hz), 1.92 (s, 1H, OH), 1.64 (pent, 2H, J = 7.3 Hz), 1.38 (sext, 1H, J = 6.9 Hz), 1.24 (sext, 1H, J = 6.9 Hz), 0.93 (m, 1H), 0.72 (m, 1H), 0.35 (q, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.49, 68.37, 52.45, 30.50, 27.74, 20.17, 18.01, 14.25; GC: HP1 (30 m × 0.32 mm × 0.25 μm), 25 psi, 200 °C front inlet. Five minutes @ 50 °C, ramp 25 °C/min to 250 °C, then hold for 4 min, t_r(**2**) = 7.15 min, t_r(*rac*-**1**) = 6.72 min.

ReactIR Monitoring of Acetylene Gas Formation in the Preparation of 2-Pent-4-ynyl-cyclopropanol (*rac*-1). To a four-necked 250-mL RBF fitted with a ReactIR probe, N_2 inlet with flow meter, condenser, and outlet to a FTIR gas cell was charged 5.0 mL of DMPU followed by **5** (0.82 g, 8 mmol). In a second two-necked 15-mL RBF equipped with a temperature probe, N_2 inlet, and septum was added 1 g of **2** (7.28 mmol, 1.0 equiv) and 3.0 mL of THF. The solution was cooled to an internal temperature of 0 °C with an ice bath. To this solution was added 2.95 mL of 33 wt % *n*-hexyllithium (7.28 mmol, 1.0 equiv) slowly via syringe pump over 1 h. Upon completion of the addition, the solution of the lithium alkoxide of **2** was transferred via cannula to the flask containing the slurry of **5** in DMPU. Upon completion of the addition, the reaction was heated to an internal temperature of 52.1 °C for 4 h to effect complete conversion. The 0.5 N HCl (17.5 mL) was added slowly, and an ice bath was applied to maintain an internal temperature below 21 °C. ReactIR monitoring of the headspace gas was continuous throughout the reaction. Acetylene gas concentrations were quantified using known mixtures of H_2 in N_2.



Preparation of Acetic Acid Racemic *trans*-2-Pent-4-ynyl-cyclopropyl Ester (*rac*-7). To a 5-L RBF equipped with a nitrogen inlet, mechanical stirrer, dropping funnel, and thermocouple under N_2 was added 31.2 g of *rac*-**1** (251 mmol, 1.0 equiv), 350 mL of MTBE, and 45.5 mL of triethylamine (327 mmol, 1.3 equiv) prior to cooling the solution in an acetone/ice bath to an internal temp of <5 °C. To the solution was added from the dropping funnel 23.7 mL of acetyl chloride (301 mmol, 1.1 equiv) over a 30-min period while maintaining the internal temp <10 °C. The resulting slurry was then warmed to room temperature and aged for 2 h. At this point, the reaction mixture was diluted with 200 mL of water. The biphasic mixture was transferred to a separatory funnel and the aqueous layer removed. The organic layer was washed with 200 mL of 2 N HCl and then with 300 mL of sat. $NaHCO_3$ prior to drying over $MgSO_4$. The solvent was removed in vacuo to give 41.8 g of *rac*-**7** (>99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dt, 1H, J = 6.7, 2.9 Hz), 2.25 (dt, 2H, J = 2.7, 7.0 Hz), 2.03 (s, 3H), 1.95 (t, 1H, J = 2.6 Hz), 1.67 (m, 2H), 1.39 (m, 2H), 1.01 (m, 1H), 0.89 (m, 1H), 0.57 (q, 1H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.60, 84.15, 68.47, 54.20, 30.12, 27.40, 20.85, 17.92, 17.83, 11.81; GC: Restek RT-Bdex SA (30 m × 0.25 mm × 0.25 μm), 60 cm/s linear velocity, 20:1 split, 120 °C isothermal, t_r(**1**) = 25.0, 29.6 min, t_r(**7**) = 17.1, 17.5 min.

Preparation of (1*R*, 2*R*)-2-Pent-4-ynyl-cyclopropanol (*ent*-1). To a 2-L round-bottom flask equipped with an overhead stirrer and temperature probe was added a 60 wt % solution of *rac*-**9** in MTBE (44.8 g, 0.27 mol) and an additional 650 mL of MTBE that had been saturated with aqueous 0.1 M pH 7 phosphate buffer, giving a final solution concentration of *rac*-**7** of 60 g/L. The flask was placed in an ice bath to maintain an internal temperature of approximately 10 °C throughout the hydrolysis reaction, which was initiated by the addition of 730 mg of Novozym 435. The reaction was aged at 10 °C for approximately 4 h until conversion had reached 41%, at which point the ee of *ent*-**1** was 96%. The reaction mixture was then filtered through a 150-mL medium-pore glass filter funnel, and the solid immobilized enzyme was washed three times with 80 mL of MTBE. The resulting MTBE solution was then solvent switched to heptane. The mixture in heptane was applied to a 120-g silica column and eluted with a 2.5 to 25.0% EtOAc in heptane gradient (v/v). The alcohol *ent*-**1** was located by TLC (silica, 20% EtOAc/heptane) and then the fractions were analyzed by GC (HP-1, 30 m × 320 μm × 0.25 μm film, 9.14 psi constant He pressure, 15:1 split, 50 °C for 5 min then 25 °C/min to 275 °C and hold 5 min, RT of alcohol 8.8 min). Clean fractions were concentrated to give 10.1 g (80 wt %, 95%ee, 30% yield from *rac*-**7**) of the desired *ent*-**1**. GC: Restek RT-Bdex SA (30 m × 0.25 mm × 0.25 μm), 60 cm/s linear velocity, 20:1 split, 120 °C isothermal, t_r(**1**) = 25.0, 29.6 min, t_r(**7**) = 17.1, 17.5 min.

■ ASSOCIATED CONTENT

Supporting Information. Copies of the NMR spectra for *rac*-**1**, **2**, **3**, and *rac*-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mails: carl_baxter2@merck.com; gbeutner@gmail.com; khateeta_emerson@merck.com.

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