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Inter- and Intramolecular Annulation Strategies to a Cyclopentanone Building Block Containing an All-Carbon Quaternary Stereogenic Center

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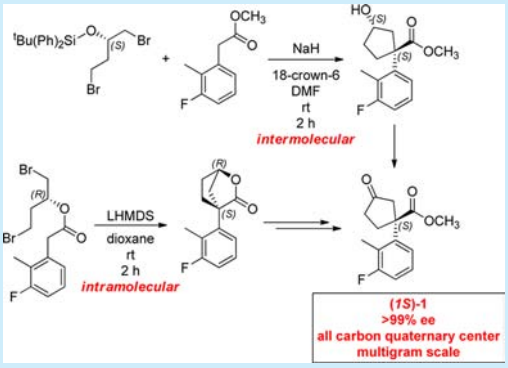
Supporting Information

ABSTRACT: Synthesis of (*S*)-2-methyl-3-fluorophenyl cyclopentanone methyl ester (1*S*)-**1** has been achieved by both inter- and intramolecular alkylation reactions on multigram scale, using chiral pool reagents. The intramolecular variant is a novel example of a chiral *bis*-electrophile reacting with a carbon nucleophile to form an enantiomerically pure all-carbon quaternary center.



One-pot, tandem reaction sequences provide an efficient strategy for the construction of complex natural product scaffolds as well as novel three-dimensional chemotypes for drug discovery.[1] Such reactions have indisputable benefits in generating complex molecules in a time- and atom-efficient manner. Herein, we report complementary tandem approaches to a synthetically challenging intermediate which incorporates a chiral quaternary carbon center within a cycloalkane ring.

As part of a recent lead optimization program, we required a multigram quantity of enantiomerically pure (*S*)-2-methyl-3-fluorophenyl cyclopentanone methyl ester (1*S*)-**1**. An extensive search of the literature provided only a limited number of routes to phenyl substituted cyclopentanone esters, commonly via hydroboration of the appropriate cyclic alkene followed by oxidation of the subsequent alcohol (Figure 1).[2] To the best of our knowledge, Hoveyda and co-workers have published the only enantioselective synthesis of a 3-carboxy-3-phenylcyclopentanone ester, utilizing a silver-NHC/diaryl zinc-mediated conjugate addition reaction.[3] This transformation, although elegant, requires a noncommercial catalyst system and the use of a glovebox. In addition, the insertion of 2-tolyl zinc reagents has not been demonstrated previously in such systems (Figure 1).

We envisaged that a tandem alkylation reaction of a substituted 2-methyl phenylacetic ester enolate with a *bis*-electrophile would provide access to **1** (Figure 2). Our initial synthesis of (*rac*)-**1**, by analogy to a described procedure,[4] used TBS-protected, commercially available (*rac*)-1,4-dibromo-2-butanol and gave a 3:1 mixture of cyclopentanol diastereomers

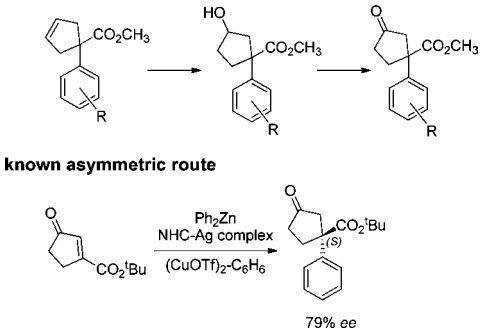


Figure 1. Synthesis of 3-aryl cyclopentanones.

indicating a modest induction of chirality at the newly formed quaternary center (Figure 2). Encouraged by this modest diastereoselectivity in our cyclization, we hoped to use a protected, enantiomerically pure 1,4-dibromo-2-butanol derivative to control the stereogenic process and the absolute configuration of the newly formed quaternary center.

Synthesis of **5** was achieved in three steps (Scheme 1).[5] In summary, the commercially available (*S*)-butane-1,2,4-triol (*S*)-**2** was selectively mesylated at the primary hydroxy groups using methanesulfonyl chloride in pyridine. Subsequent silylation of secondary alcohol **3** with TBDPS chloride incorporated the sterically demanding protecting group to give dimesylate **4** in

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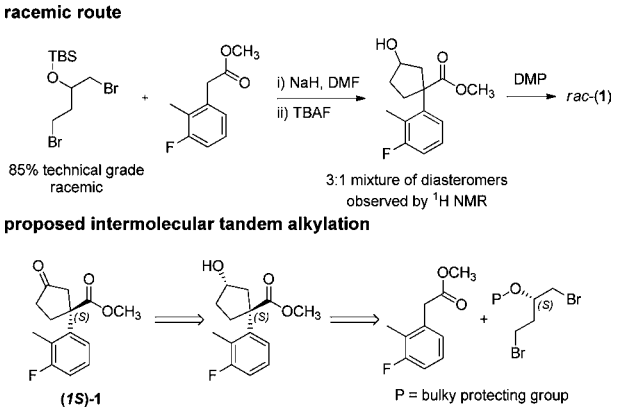
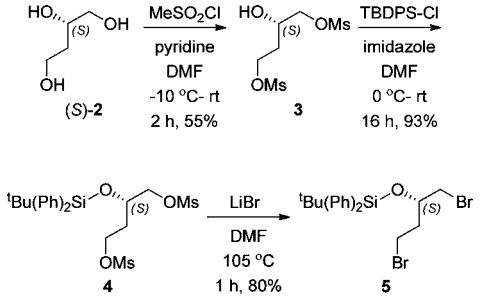


Figure 2. Proposed route.

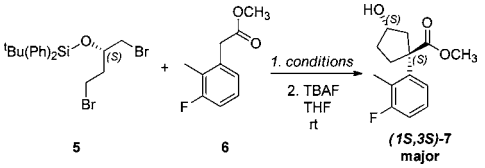
Scheme 1. Synthesis of Silyl Protected Dibromide



high yields. Finally, displacement of the mesylate groups with lithium bromide provided the desired electrophile **5** which was critical for exploring the intermolecular tandem alkylation.

Based on our previous results, we anticipated that reaction of **5** with the enolate form of **6** would give the silyl-protected cyclopentanol with modest diastereoselectivity. Conditions for the tandem alkylation reaction are outlined in Table 1. The crude cyclization product was treated with TBAF to remove the silyl group, and the diastereomeric ratio of the crude alcohols **7** was determined by comparison of integrals of the two diastereomers in the ^{19}F NMR spectrum.[6]

Table 1. Conditions for Intermolecular Alkylation



entry	base	solvent	temp, °C	additive[a]	yield, %[b]	dr[c]
1	KO^{t}Bu	toluene	90	–	0	N/A
2	LHMDS	THF	−78	–	0	N/A
3	NaH	DMF	−20	KI	42	4:1
4	NaH	DMF	0	KI	35	5:1
5	NaH	DMF	20	KI	18	7:1
6[d]	NaH	DMF	20	KI	80	6:1
7	NaH	DMF	20	18-C-6	64	7:1
8[e]	**NaH**	**DMF**	**20**	**18-C-6**	**85**	**9:1**

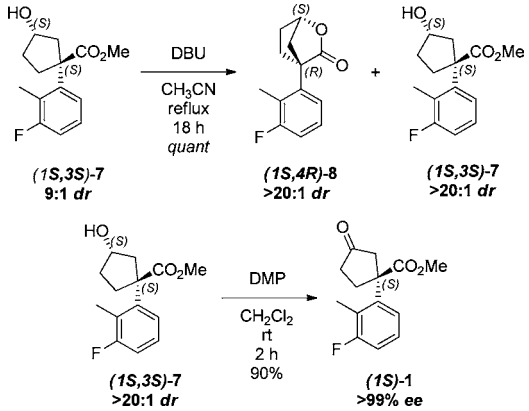
[a]Used 2 equiv of KI or 10 mol % 18-C-6. [b]Isolated yield on 10 mmol scale based on a 1:1 ratio of **5** and **6**. [c]Ratio of diastereomers based on ^{19}F NMR - minor isomer (1*R*,3S)-7. [d]Used 2 equiv of **5**. [e]Portionwise addition of NaH over 2 h.

Our preliminary efforts to couple **5** and **6** using either potassium *tert*-butoxide at high temperatures (90 °C, 6 h, entry 1) or lithium hexamethyldisilazide (−78 °C, warming to rt over 6 h, entry 2) gave no conversion to **7**. Gratifyingly, the use of sodium hydride at −20 °C in the presence of potassium iodide to activate the electrophile furnished the desired cyclopentane **7** in reasonable yield and diastereomeric ratio (entry 3). The reaction appeared to proceed with increased diastereoselectivity at higher temperatures (4:1 to 7:1 *dr*, entries 3−5). Although this improved selectivity was encouraging, the yields remained low.

The yield of cyclopentanol **7** was significantly improved by doubling the quantity of dibromide **5**, which gave **7** in 80% yield (6:1 *dr*, entry 6). In order to optimize atom efficiency, we reverted to 1 equiv of **5** and added a catalytic quantity of 18-crown-6 to activate the enolate, which led to an increased yield without loss of diastereoselectivity (entry 7). In the literature it has been observed that adding crown ethers in catalytic quantities enhances the reactivity of enolates to alkylation by complexing the sodium ion.[7] Optimum conditions were obtained by portionwise addition of sodium hydride to provide a low concentration of free base and afforded cyclopentane **7** in both excellent yield and selectivity (85%, 9:1 *dr*, entry 8).

The major isomer of the 9:1 mixture of **7** could be isolated in milligram quantities by careful flash chromatography. However, on a larger scale this became a protracted process. We hypothesized that the undesired diastereomer of **7** had an ideal conformation to undergo intramolecular lactonization, whereas the desired isomer did not. Indeed, on refluxing a mixture of cyclopentanols **7** in the presence of DBU, quantitative conversion of minor isomer (1*R*,3*S*)-**7** to lactone (1*S*,4*R*)-**8** was observed whereas the alcohol (1*S*,3*S*)-**7** remained unchanged (Scheme 2). The polarity difference between

Scheme 2. Intramolecular Cyclization of 7 to Lactone 8



(1*S*,3*S*)-**7** and (1*S*,4*R*)-**8** greatly simplified purification on a gram scale. (1*S*,3*S*)-**7** was treated with Dess-Martin periodinane to give the desired ketone (1*S*)-**1** in 90% yield and >99% *ee*.

Encouraged by the facile nature of the intramolecular lactonization step to generate (1*S*,4*R*)-**8**, we considered whether the diastereomer of lactone **8** could serve as an intermediate for an alternative route to our desired ketone building block. Hence we envisaged that the intramolecular cyclization of an enantiomerically pure (*R*)-1,4-dibromo-2-butanol derivative tethered via an ester linkage to the phenylacetic acid moiety would lead to the bicyclic lactone (1*R*,4*S*)-**8** in a highly stereoselective manner (Scheme 3).

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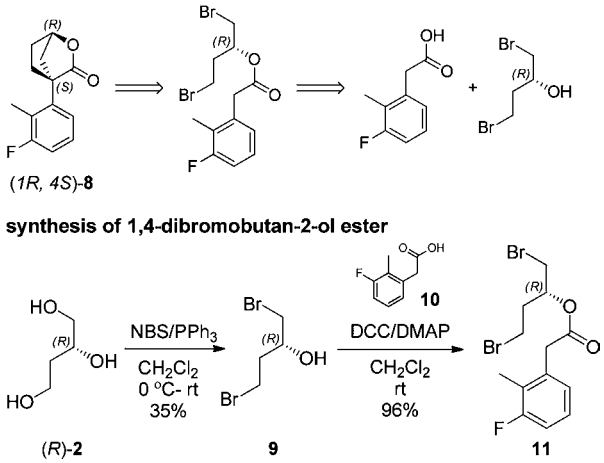
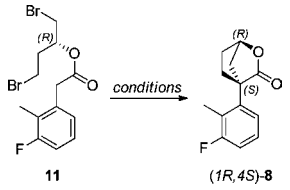
Scheme 3. Synthesis of (*R*)-1,4-Dibromobutan-2-ol Ester 11



Thus, (*R*)-1,4-dibromobutan-2-ol (**9**) was synthesized from (*R*)-butane-1,2,4-triol ((*R*)-**2**)[8] by a modified Appel reaction ($NBS/PPh_3/CH_2Cl_2$). Subsequent coupling of **9** to 2-(3-fluoro-2-methylphenyl) acetic acid (**10**) using DCC/DMAP gave the desired (*R*)-1,4-dibromobutan-2-ol ester **11**.

Results for the *O*-tethered tandem alkylation approach are summarized in Table 2. Preliminary attempts at lactonization

Table 2. *O*-Tethered Tandem Alkylation Approach



entry	base	solvent	temp, °C	yield, %[a,b]
1	NaH	DMF	20	0
2	LHMDS	DMF	0–20	0
3	LHMDS[c]	THF	0–20	40
4	**LHMDS[c]**	**dioxane**	**20**	**73**

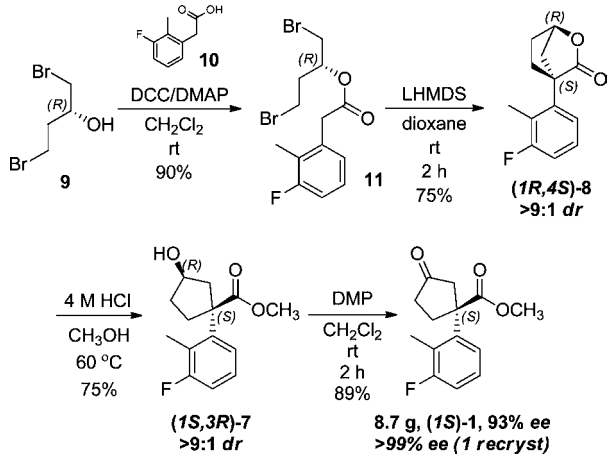
[a]Isolated yield on 10 mmol scale. [b]Isolated as a single diastereomer. [c]LHMDS (2.2 equiv) added at a rate of 1 mmol/min.

using sodium hydride or lithium hexamethyldisilazide in DMF at 20 °C gave no conversion to (1*R*,4*S*)-**8** (entries 1, 2). However, using LHMDS in THF afforded a single diastereomer of (1*R*,4*S*)-**8** in modest yield after 2 h (entry 3). Switching solvent to 1,4-dioxane and using a concentration of 0.1 M **11** with addition of LHMDS (2.2 equiv) in THF at a rate of 1.0 mmol/min resulted in complete consumption of **11** in 2 h and formation of the product (1*R*,4*S*)-**8** in an isolated yield of 73% (entry 4). The reproducibility of this yield was highly dependent on the rate of addition of LHMDS, and slower addition rates led to a mixture of products.

To explain the diastereoselective formation of (1*R*,4*S*)-**8**, we rationalized that the order of formation of either the five- or six-membered lactone is inconsequential, as both alkylation pathways would result in the desired product. Similarly, there was no requirement to control the bond geometry of the initial ester enolate, as the resulting stereocenter will be eliminated upon formation of the subsequent enolate. Chirality at the quaternary center can then be induced by diastereofacial addition of the second alkyl halide partner to the conformationally locked cyclic ester enolate.

The *O*-tethered tandem alkylation protocol was repeated on a 14 g scale of dibromide **9** to give the lactone (1*R*,4*S*)-**8** in a highly efficient manner, as shown in Scheme 4. Ring opening of

Scheme 4. Tethered Synthesis on Multigram Scale



lactone (1*R*,4*S*)-**8** with methanol under acidic conditions gave cyclopentanol (1*S*,3*R*)-**7** which was converted to 8.7 g of desired ketone (1*S*)-**1** in 89% yield and 93% *ee*. Finally, recrystallization of (1*S*)-**1** from heptane enhanced the enantiomeric purity to >99% *ee*.

In summary, a tandem alkylation approach, as well as a novel *O*-tethered tandem alkylation protocol, have been developed using readily available chiral pool intermediates. Both reactions allow for the multigram synthesis of the key cyclopentanone intermediate (1*S*)-**1**. To the best of our knowledge, the *O*-tethered tandem conversion of the dibromide **11** to lactone **8** is the first example of its type and provides a powerful method of forming enantiomerically pure cyclopentanes incorporating quaternary carbon centers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of the ^1H, ^{13}C, ^{19}F NMR spectra, and chiral SFC data (where appropriate) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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