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Regioselective aldol condensations of a cholestanone-derived dialdehyde: new twists on a classic reaction

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Abstract—Methods have been developed for the regioselective formation of both aldol condensation products from a non-symmetrical dialdehyde derived from 5α-cholestan-3-one. The findings disclosed herein, as well as their mechanistic implications, should assist in achieving selective intramolecular aldol closures in other contexts.

For well over 50 years, intramolecular aldol condensations have served as one of the most powerful tools for the synthesis of functionalized ring systems.[1] Indeed, examples of these reactions, particularly of the Robinson annulation type,[2] are legion. Nevertheless, gaps still remain, most prominently in terms of our ability to generate both possible aldol condensation products from non-symmetrical substrates with high levels of control. For example, our group's total synthesis of gibberellic acid (**3**, Scheme 1)[3] and the Woodward synthesis of steroids[4] featured aldol condensations that led to a single product (i.e., **2** and **5**) by virtue of substrate bias reinforced by judicious reagent choice. Overturning such bias has historically proven difficult to achieve.[5] As part of a recent research program in total synthesis,[6] we needed to accomplish just such an outcome with a substrate possessing the general architecture of dialdehyde **7**. Within this communication, we report some of our studies toward this objective, experimentation that has led to conditions capable of forming both **8** and **9** in moderate to good yield with up to 50:1 selectivity.

As indicated in Scheme 1, the test substrate **7** was prepared from commercially available 5α-cholestan-3-one (**6**) via initial hydroxylation at C-2 though an L-proline-catalyzed nitroso aldol reaction with nitrosobenzene,[7] followed by $NaBH_4$-mediated diol formation and $NaIO_4$ cleavage (49% overall yield). Although these operations appear routine, it is worth noting that in the initial step the C-2 hydroxyl was installed exclusively from the α-face, and that this reaction could be induced to proceed to completion without the need for syringe pump addition of nitrosobenzene simply by adding a few drops of AcOH to the reaction mixture. In the absence of this acid activator, the reaction typically stalled at 50–60% conversion even though 2 equiv of the oxygen source was used.

Our initial efforts to achieve selective aldol condensation focused on the conversion of **7** into cyclopentene **8**, the product that we anticipated to be the easier of the two to access, given that it could result from nucleophilic attack of an enamine of the less hindered formyl onto the other carbonyl, followed by dehydration. Indeed, as indicated in Table 1, both the Woodward conditions (piperidinium acetate, entry 1) as well as exposure to dibenzylammonium trifluoroacetate (entry 2) in benzene at 25 °C afforded **8** with good selectivity (4:1 and 6:1, respectively) in good yield (61% and 68%, respectively). In an effort to improve upon these results, we then screened dibenzylammonium trifluoroacetate with a variety of more polar solvents, given the reported impact of solvent on the cyclization selectivity with piperidinium acetate.[8] None of the conditions tested (entries 3–9) provided superior results; in fact, greater solvent polarity abolished selectivity (entries 8 and 9). We also attempted to employ bulkier variants of the activating salt, such as phenylbenzylammonium trifluoroacetate (entry 10) and dicyclohexylammonium trifluoroacetate (entry 11),[9] but no further improvement was noted.

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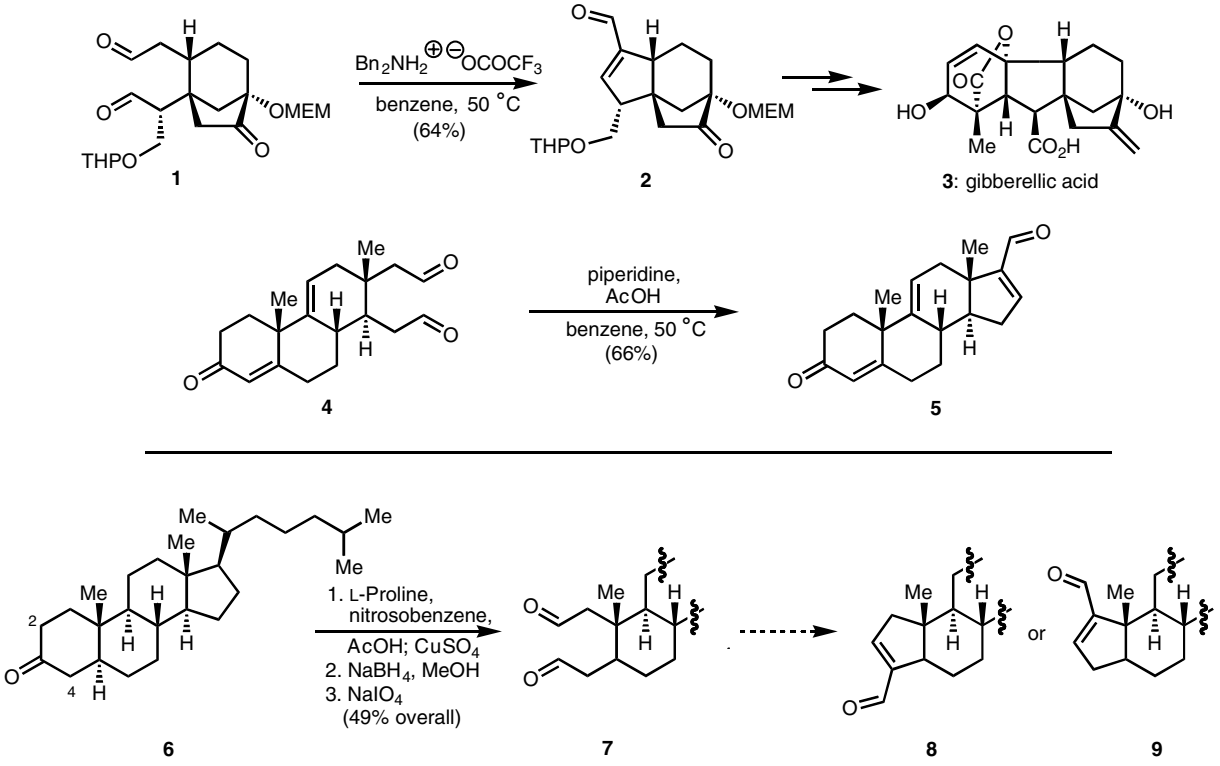


Scheme 1. Historical precedent for aldol condensations of non-symmetrical dialdehydes and the goal of this work: selective formation of **8** and **9** from **7**.

Table 1. Aldol cyclization/dehydration reactions of dialdehyde **7**[a]

Entry	Conditions	Ratio of **8**:**9**	Yield (%)
1	Piperidine (cat.), AcOH (cat.), benzene, 25 °C, 15 min; 55 °C, 75 min	4:1	61
2	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), benzene, 25 °C, 12 h	6:1	68
3	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), CH_2Cl_2, 25 °C, 12 h	4:1	57
4	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DME, 25 °C, 12 h	3:1	59
5	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), THF, 25 °C, 12 h	2:1	59
6	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DME/HMPA (1:1), 25 °C, 12 h	2:1	66
7	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), THF/HMPA (1:1), 25 °C, 12 h	2:1	62
8	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), HMPA, 25 °C, 12 h	1.3:1	59
9	$Bn_2NH_2^{+-}OCOCF_3$ (3.0 equiv), DMSO, 25 °C, 12 h	1.1:1	60
10	$PhBnNH_2^{+-}OCOCF_3$ (5.0 equiv), benzene, 25 °C, 30 min; 50 °C, 1 h	5:1	56
11	$(Cyclohexyl)_2NH_2^{+-}OCOCF_3$ (5.0 equiv), benzene, 25 °C, 30 min; 50 °C, 5 h	2:1	24
12	Morpholine (6.0 equiv), octanoic acid (7.0 equiv), HMPA (1.5 equiv), Et_2O, 0 °C, 20 h	50:1	44
13	D-Proline (5.0 equiv), DMSO, 25 °C, 10 h	1:2	48
14	L-Proline (5.0 equiv), DMSO, 25 °C, 10 h	1:2	52
15	(*S*)-Indoline-2-carboxylic acid (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	1:50	47
16	D-Proline (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	8:1	17
17	L-Proline (5.0 equiv), $MeCN/CH_2Cl_2$ (1:1), 25 °C, 10 h	1:2	16

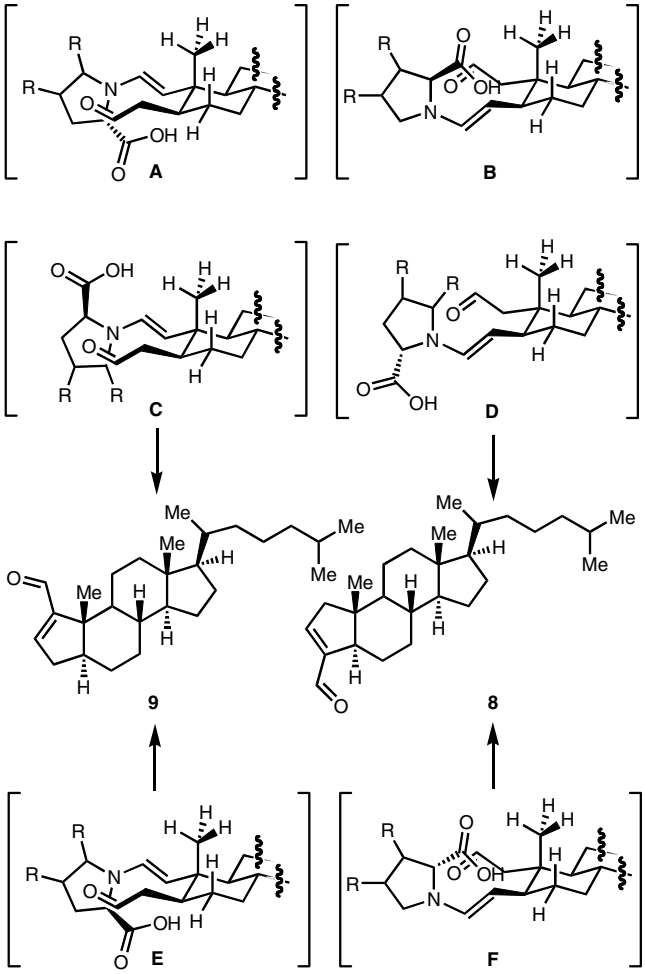
[a] Substrate concentration was 0.01–0.02 M in each case.

The critical issue for our study, however, was not whether we could form **8** with high levels of control, but whether we could reliably access aldol product **9**. Our first attempt in this direction examined conditions[5c] developed by the Inubushi group over 20 years ago to similarly overturn high levels of selectivity as achieved with both piperidinium acetate and dibenzylammonium trifluoroacetate on a non-symmetrical dialdehyde substrate: morpholine (6.0 equiv), octanoic acid (7.0 equiv), and HMPA (1.5 equiv) in Et_2O at 0 °C. Surprisingly, however, these conditions led to selective formation of aldol adduct **8** in 44% yield when applied to dialdehyde **7** (entry 12). The published mechanistic rationale[5c] for the behavior of this specialized set of reagents was clearly not appropriate.

Nevertheless, we expected that success could still be achieved by turning to Hajos–Parrish-type (proline) catalysts. Based on recent experimental[10] and theoretical[11] work, which has established that intramolecular aldol reactions of the Robinson type driven by these reagents proceed via an enamine mechanism involving a single

amino acid molecule with the C–C bond-forming step being the rate-determining one, we expected that **7** might be well poised to afford aldol product **9** preferentially. As indicated in Scheme 2, using an L-proline-derived template for purposes of illustration (R = H), there are four possible enamines (**A**, **B**, **C**, and **D**) that can be formed from dialdehyde **7**. Of these, **C** and **D** should be more likely to lead to the product given their ability to achieve an activating hydrogen-bond between the carboxylate residue of the amino acid and the remaining aldehyde. Based on molecular models, however, such an interaction is more readily achievable within assembly **C**. Consequently, **9** should be the predominant product even though enamine **C** requires reaction of the amino acid with the more hindered aldehyde. Similar arguments predict that a D-proline-catalyzed reaction would afford **9** with equal facility by way of enamine **E**.

As revealed by entries 13 and 14 in Table 1, this overall picture would appear to be accurate as exposure of **7** to either D- or L-proline in DMSO at ambient temperature indeed led to a reversal in selectivity favoring **9** by a 2:1 margin over **8** in good yield (48% and 52%, respectively). To our delight, exposure of **7** to (*S*)-indoline-2-carboxylic acid in $MeCN/CH_2Cl_2$ (1:1) led to the formation of **9** in 44% yield with better than 50:1 selectivity (entry 15). This outcome is also consistent with the picture presented in Scheme 2 as destabilizing steric interactions between the extra bulk at the positions denoted by R and the axially-disposed ring-junction methyl group of the cholestanone framework would substantially favor enamine **C** over **D** as the dominant reactive pathway in comparison to simple L-proline. It is important to note, however that the amino acid must be soluble in the reaction media for the picture within the confines of Scheme 2 to have predictive power. For instance, exposure of **7** to either D- or L-proline in $MeCN/CH_2Cl_2$, media in which the amino acid is fully insoluble, led to a far different set of results (entries 16 and 17). At present, we believe these unique outcomes separately favoring the two aldol adducts reflects some type of heterogeneous surface effect. It is evident that the low yields in these cases stem from poor conversion over the reaction time in these experiments, rather than an inherent deficiency of the reactions themselves.



Scheme 2. Proposed enamine transition state models to account for the selective formation of either **8** or **9**.

In conclusion, we were able to achieve the controlled formation of both aldol adducts (**8** and **9**) from nonsymmetrical aldehyde **7** with better than 50:1 selectivity. Hopefully, these results should assist in achieving regioselective intramolecular aldol closures in other contexts. Of particular note within this work is the demonstrated ability of chiral amino acids to overturn inherent substrate/reagent bias found in more classical approaches to this problem, which, although studied long ago to achieve stereoselective Robinson annulations,[12] has not been explored to any serious extent with dialdehyde substrates until now.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.136.

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