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Diastereoselective synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones via SmI_2-mediated reductive coupling of 2-alkylacrylates of *N*,*N*-diisopropyl-2-hydroxybenzamide with aldehydes

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ABSTRACT

Samarium(II) diiodide has been used to mediate reductive coupling reactions of aldehydes with a variety of substituted acrylates, in both achiral and chiral forms, for accessing substituted dihydrofuran-2(3*H*)-ones (γ-butyrolactones). Two major issues, concerning with self-dimerization of α-non-branched aliphatic aldehydes and low diastereoselectivity of the products, render limited application of the reductive coupling protocol in total synthesis of natural products. We report here on a novel type of substituted acrylates derived from the 2-amido arenols (HO-Ar^{am}) such as *N*,*N*-diisopropyl-2-hydroxybenzamide. The acrylates of HO-Ar^{am} enable: (a) preferential conjugate reduction of the acrylates than carbonyl reduction of aliphatic aldehydes, leading to diminished aldehyde self-dimerization; and (b) organization of an eight-membered ring among the amide carbonyl oxygen atom and samarium(III) to form a 7/8-bicyclic transition state, resulting in highly diastereoselective protonation of the samarium(III) enolate intermediate. Examples of synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones from 2-alkylacrylates of HO-Ar^{am} and aliphatic aldehydes are provided.

1. Introduction

Samarium(II) diiodide (SmI_2, Kagan's reagent) has been widely used as an efficient reductant in facilitating various organic transformations.[1] One major utility of the SmI_2-mediated reactions is the reductive couplings for carbon–carbon bond formation. Although the intramolecular reductive couplings mediated by SmI_2 have enjoyed applications in total synthesis of natural products,[1e,g,k] the intermolecular reductive cross-coupling of carbonyl compounds with conjugate alkenes using SmI_2 remains challenging.[1m] In 1986, Fukuzawa[2] and Inanaga[3] independently reported the cross-coupling reactions of substituted acrylates **1** and **3** with aldehydes in the presence of SmI_2 and an alcohol (as the proton source) to afford substituted dihydrofuran-2(3*H*)-ones (γ-butyrolactones) **2a**,**b** and **4a**,**b** in 70–75% yields (Scheme 1). However, the diastereoselectivity of the products varies from 70:30 to 95:5 in terms of the structures of both acrylates and aldehydes. In 1997, Fukuzawa and co-workers[4] reported the first enantioselective reductive coupling reaction of the *N*-methylephedrine-derived chiral crotonate **5a** with aliphatic aldehydes to produce chiral dihydrofuran-2(3*H*)-ones **6** in both high *cis*:*trans* ratios and high enantioselectivity (93–97% ee) (Scheme 2). However, the product yields as estimated by GC analysis are moderate (57–74%). Procter and co-workers[5] disclosed the Wang resin-bound chiral crotonate **5b** and the fluorous-tagged chiral crotonate **5c** for the reductive coupling reactions with aliphatic aldehydes, obtaining the products **6** in both high *cis*:*trans* ratios and high enantioselectivities (88–99% ee) albeit in low to moderate isolated yields (43–82%). In our previous work,[7a] we developed a novel class of chiral crotonate **5d**, which was derived from the atropisomeric 2-hydroxy-8-methoxy-1-naphthamide.[7b] The SmI_2-mediated reductive coupling of **5d** with aliphatic aldehydes gave the chiral products **6** in good *cis*:*trans* ratios (72:28–91:9) and high enantioselectivities (97–99%). Moreover, the isolated product yields of 81–90% are much higher than those obtained with the crotonates **5a**–**c**.

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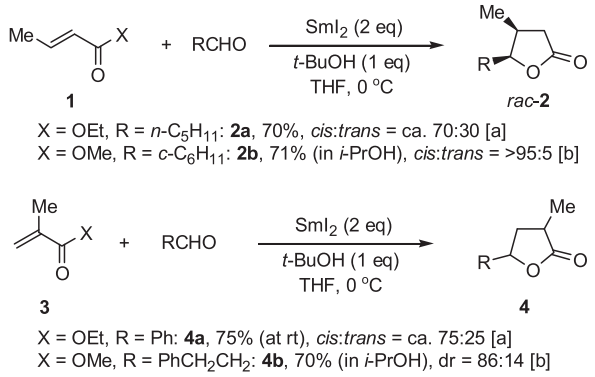
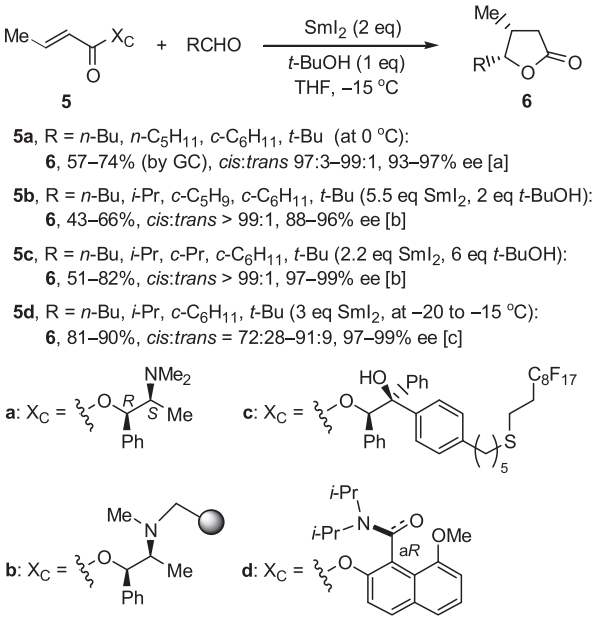
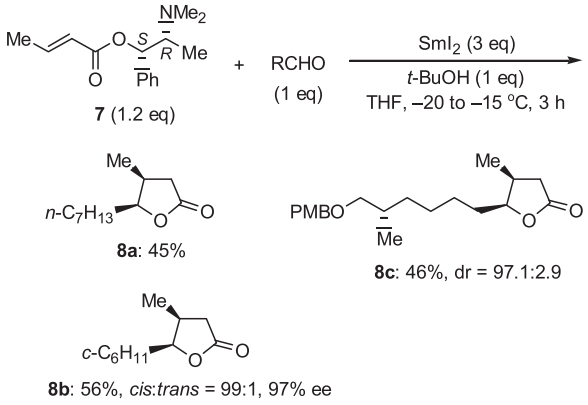


Scheme 1. SmI_2-mediated reductive coupling of the substituted acrylates **1** and **3** with aldehydes reported by Fukuzawa [a; Ref. 2] and Inanaga [b; Ref. 3].



Scheme 2. Reductive coupling of the chiral crotonates **5** with aldehydes reported by Fukuzawa [a; Ref. 4], Procter [b; Refs. 5 and 6], and Dai [c; Ref. 7].

Low product yields are the drawback for accessing the chiral *cis*-4,5-disubstituted dihydrofuran-2(3*H*)-ones **6** from the *N*-methylephedrine-derived chiral crotonate **5a** and it hampered general applications of this highly enantioselective reaction. In our effort in synthesis of the 2,3,5-trisubstituted tetrahydrofuran fragment[8] of amphidinolide T family of congeners, the chiral compound **8c** was prepared from the reductive coupling of the *N*-methylephedrine-derived chiral crotonate **7** with the corresponding α-non-branched aldehyde in 46% isolated yield on a 3 mmol scale under the optimized conditions (Scheme 3). Similarly, the reaction of **7** with *n*-octanal furnished the product **8a** in 45% isolated yield. When cyclohexanecarboxaldehyde was used, the product **8b** was formed in a slightly higher yield (56%). We found that the main byproduct in the reductive coupling reaction of α-non-branched aliphatic aldehydes with **7** was the dimers of the aldehyde. The undesired dimerization pathway might be suppressed for the ketyl radical generated from α-branched aliphatic aldehydes. In order to address both issues of low product yield and low stereoselectivity associated with SmI_2-mediated reductive coupling of substituted acrylates with aliphatic aldehydes, we have introduced a novel class of substituted acrylates derived from the 2-amido arenols (HO-Ar^{am}) such as *N*,*N*-diisopropyl-2-hydroxybenzamide. We report here on the

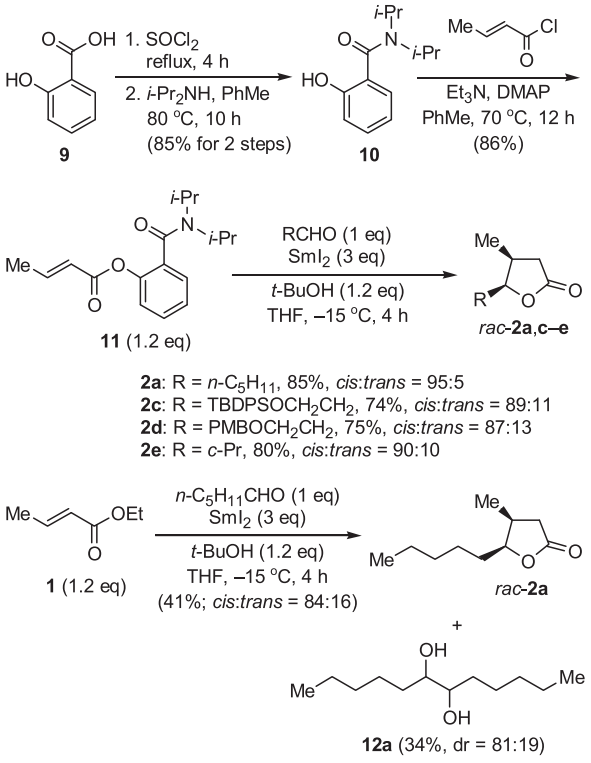


Scheme 3. Reductive coupling of **7** with aldehydes reported by Dai.

results of the highly diastereoselective synthesis of *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones.

2. Results and discussion

In our previous work, as mentioned in Scheme 2, the reactions of the chiral 1-amido-2-naphthol-derived crotonate **5d** with aliphatic aldehydes afforded higher product yields. We attributed the results to the electron-withdrawing nature of the 1-amido-2-naphthol moiety,[9] which might favor for conjugate reduction of the crotonate over carbonyl reduction of the aldehyde. Consequently, the undesired self-dimerization of the aldehyde partner via the ketyl radical could be minimized. Therefore, we envisioned that the crotonate **11** derived from a simpler 2-amido arenol, i.e., *N*,*N*-diisopropyl-2-hydroxybenzamide (**10**) should be a useful substrate for the synthesis of racemic *cis*-5-alkyl-4-methyldihydrofuran-2(3*H*)-ones *rac*-**2a**,**c**–**e** (Scheme 4). Starting from salicylic acid (**9**), the 2-amido phenol **10** was prepared in 85% overall yield by treating **9** in refluxing $SOCl_2$ and subsequent amidation of the resultant acyl chloride with *i*-Pr_2NH in PhMe at 80 °C. Reaction of **10** with crotonoyl chloride in the presence of Et_3N and catalytic DMAP in PhMe at 70 °C for 12 h furnished the crotonate **11** in 86% yield. Three aliphatic α-non-branched aldehydes, *n*-hexanal, $TBDPSOCH_2CH_2CHO$, and $PMBOCH_2CH_2CHO$, were subjected to the SmI_2-mediated reductive coupling with **11** to afford the products *rac*-**2a**, *rac*-**2c**, and *rac*-**2d** in 85%, 74%, and 75% yields, respectively, and in diastereomeric ratios of 87:13–95:5. For comparison purpose, we repeated the reductive coupling of ethyl crotonate (**1**, *X*=OEt) with *n*-hexanal (Scheme 1).[2] Under our conditions,[8] the product *rac*-**2a** was isolated in 41% yield and in a *cis*:*trans* ratio of 84:16 along with the dimer byproducts **12a** (34%; dr=81:19) (Scheme 4). These results are different from those as originally reported by Fukuzawa in Scheme 1.[2] Also, the product yields of *rac*-**2a**,**c**,**d** obtained from **11** are much better than the yields for the chiral compounds **6** and **8a**–**c** synthesized from the chiral crotonates **5a**–**c** and **7** derived from *N*-methylephedrine and the related 1,2-amino alcohol or 1,2-diol (Schemes 2 and 3).[4–6,8] Therefore, it can be concluded that the undesired dimerization of the aliphatic α-non-branched aldehydes in the SmI_2-mediated reductive coupling reactions could be minimized or suppressed by using the crotonate **11** derived from the 2-amido arenol **10** via preferential conjugate reduction of the crotonate **11**. Another piece of evidence was obtained from the reductive coupling of cyclopropanecarboxaldehyde with **11**. The expected product, *cis*-5-cyclopropyl-4-methyldihydrofuran-2(3*H*)-one (*rac*-**2e**),[6] was formed in 80% isolated yield as a 90:10 mixture of *cis* and *trans*

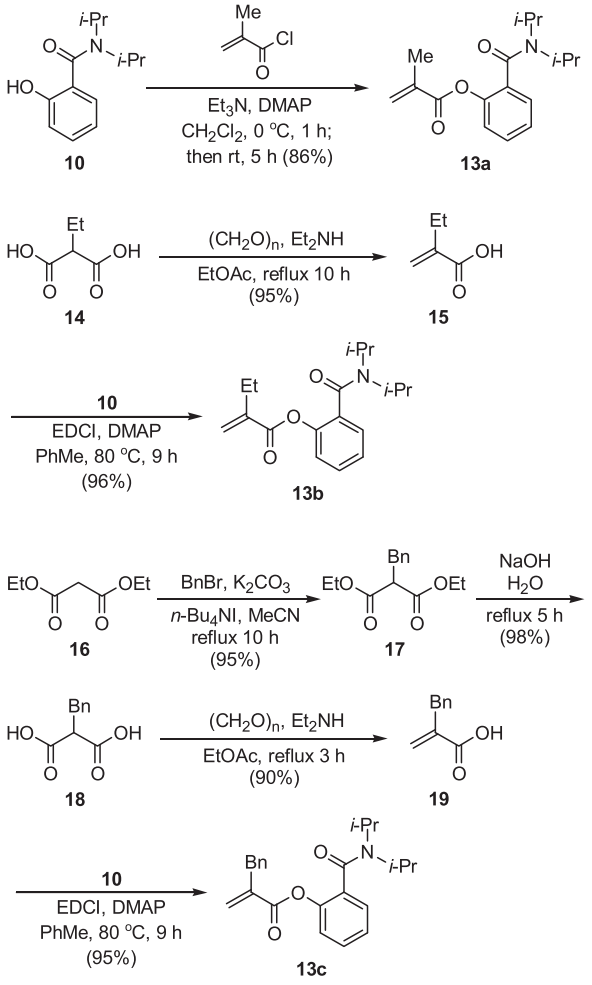


Scheme 4. Reductive coupling of the crotonates with aldehydes.

isomers (Scheme 4). Therefore, the preferential conjugate reduction of the crotonate **11** has been confirmed.

Mikami and Yamaoka[10] reported reductive coupling of methyl methacrylate (**3**, *X*=OMe) with methyl aryl ketones in the presence of 2 equiv each of SmI_2, (*R*)-BINAPO, and *t*-BuOH in THF at −78 °C to form the chiral 4,5,5-trisubstituted dihydrofuran-2(3*H*)-ones in 42–46% yields and in *cis*:*trans* ratios of 51:49–66:34 with 77–89% ee for the major isomers. Lin and co-workers[11] carried out extensive studies on the reactions of chiral and achiral methacrylates with ketones in the presence of a chiral proton source. High product yields and high enantioselectivities were obtained for some cases but the *cis*:*trans* ratios are generally low for the reactions of unsymmetrical ketone substrates. In contrast to ketones, reductive coupling of 2-alkylacrylates with aldehydes mediated by SmI_2 has not been well explored except for few cases using methacrylates **3** (Scheme 1).[2,3]

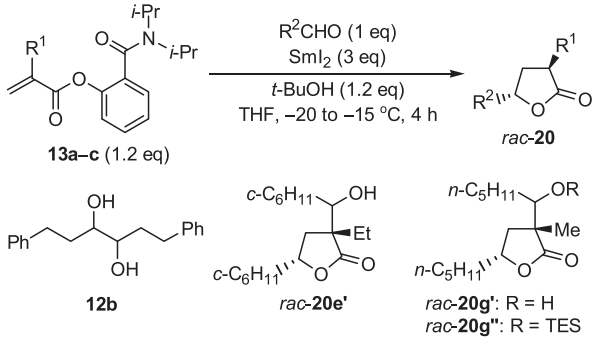
We decided to investigate the diastereoselectivity of the reductive coupling reactions of 2-alkylacrylates of **10** with aldehydes. Three 2-alkylacrylates **13a–c** were prepared as depicted in Scheme 5. The methacrylate **13a** was obtained in 86% yield by the reaction of the 2-amido phenol **10** with methacryloyl chloride in the presence of Et_3N and catalytic DMAP in CH_2Cl_2 at 0 °C to room temperature. The known 2-ethylacrylic acid (**15**),[12] prepared from ethylmalonic acid (**14**) under the Mannich reaction conditions, was subjected to the esterification with **10** using EDCI–DMAP in PhMe at 80 °C for 9 h to form the 2-ethylacrylate **13b** in 96% yield. Benzylmalonic acid (**18**) was prepared from diethyl malonate (**16**) via benzylation of **16** and subsequent saponification of diethyl benzylmalonate (**17**) in excellent overall yield. The Mannich reaction of **18** in the presence of paraformaldehyde and Et_2NH in refluxing EtOAc gave benzylacrylic acid (**19**) in 90% yield. Esterification of **19** with **10** under the same EDCI–DMAP conditions afforded 2-benzylacrylate **13c** in 95% yield.



Scheme 5. Preparation of 2-alkylacrylates **13a–c** of the 2-amido phenol **10**.

Reductive coupling reactions of 2-alkylacrylates **13a–c** were examined with four representative aliphatic aldehydes and the results are summarized in Table 1. For comparison purpose, we first carried out the reaction of methyl methacrylate (**3**, *X*=OMe) with the non-enolizable trimethylacetaldehyde and the product *rac*-**20a** was formed in 80% yield but in a non-diastereoselective fashion (entry 1, Table 1). In a sharp contrast, the same aldehyde underwent the reductive coupling reactions with the 2-alkylacrylates **13a–c** to give the products *rac*-**20a–c** in both high chemical yields and high *trans*:*cis* ratios (entries 2–4, Table 1). Similar results were obtained for the reactions of cyclohexanecarboxaldehyde with **13a–c** (entries 5–7, Table 1) except for that a minor aldol byproduct *rac*-**20e′** was obtained in 6% yield (entry 6, Table 1). As mentioned in Scheme 1, Inanaga and co-workers reported a diastereomeric ratio of 86:14 for the product *rac*-**4b** (70% yield) formed from the α-non-branched aldehyde, $PhCH_2CH_2CHO$, and methyl methacrylate (**3**, *X*=OMe).[3] We repeated the same reaction under our conditions and obtained a much lower yield of *rac*-**4b** (27%) and a lower dr value of 74:26 (entry 8, Table 1). It should be emphasized that the dimers **12b** (dr=74:26) of the α-non-branched aldehyde were isolated in 30% combined yield, echoing with the same phenomenon observed for the reductive coupling of the crotonate **1** with α-non-branched aldehydes (Scheme 4). By using the 2-amido arenol-derived methacrylate **13a**, the product *rac*-**4b** was produced in low isolated yields of 30–37% in two parallel runs but with an excellent *trans*:*cis* ratio of 96:4 (entry 9, Table 1). Although the diol

Table 1
Results of SmI_2-mediated reductive coupling of **13a**–**c** with aldehydes

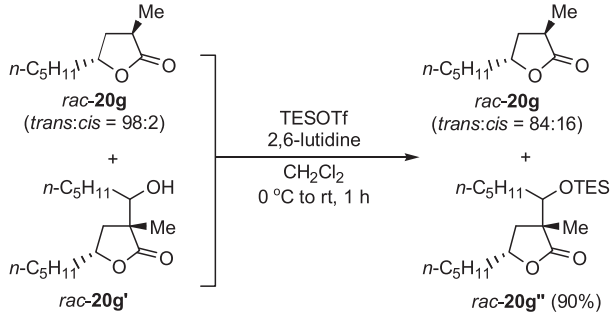


Entry	2-Alkylacrylate	R^2	Yield (%)[a]	*trans*:*cis*[b]
1	**3** (*X*=OMe)	*t*-Bu	*rac*-**20a**: 80	50:50
2	**13a**: R^1=Me	*t*-Bu	*rac*-**20a**: 95	98:2
3	**13b**: R^1=Et	*t*-Bu	*rac*-**20b**: 82	95:5
4	**13c**: R^1=Bn	*t*-Bu	*rac*-**20c**: 86	90:10
5	**13a**: R^1=Me	*c*-C_6H_{11}	*rac*-**20d**: 80	97:3
6	**13b**: R^1=Et	*c*-C_6H_{11}	*rac*-**20e**: 87[c]	95:5
7	**13c**: R^1=Bn	*c*-C_6H_{11}	*rac*-**20f**: 99	92:8
8	**3** (*X*=OMe)	$PhCH_2CH_2$	*rac*-**4b**: 27[d]	74:26
9	**13a**: R^1=Me	$PhCH_2CH_2$	*rac*-**4b**: 30–37[e]	96:4
10	**13a**: R^1=Me	*n*-C_5H_{11}	*rac*-**20g**: 40[f]	98:2

[a] Isolated yields based on amount of the aldehyde used.
[b] Estimated by ^{1}H NMR spectroscopic analysis of the crude product.
[c] The aldol product *rac*-**20e**′ was isolated in 6% yield.
[d] A 74:26 mixture of the dimers **12b** was isolated in 30% yield.
[e] A nearly equal amount of an aldol byproduct was found in the ^{1}H NMR spectra of the crude product. The aldol byproduct is inseparable from the regenerated **10**.
[f] The aldol byproduct *rac*-**20g**′ was isolated, after converting into its TES ether *rac*-**20g**″, in 30% yield as a single diastereomer.

byproducts **12b** were not detected in the reaction of **13a** with $PhCH_2CH_2CHO$ by TLC analysis of the reaction mixture an aldol byproduct was found in the ^{1}H NMR spectra of the crude product in an analogous manner to the reaction given in the entry 10 of Table 1. Due to the fact that the aldol byproduct is not separable from the regenerated **10**, the structure of the assumed aldol byproduct has not been fully confirmed.

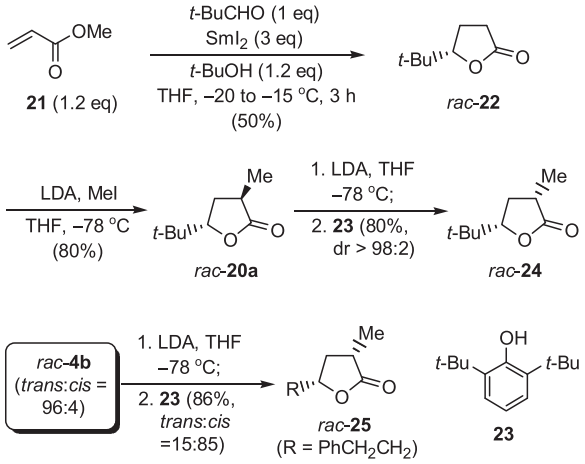
The unsatisfactory results with hydrocinnamaldehyde prompted us to conduct the reaction of **13a** with another simple linear aliphatic aldehyde (entry 10, Table 1). Under the same reductive coupling conditions, the expected *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-one *rac*-**20g** was formed from **13a** and *n*-hexanal in 40% yield along with an aldol byproduct *rac*-**20g**′ in 30% yield as estimated by ^{1}H NMR analysis. Because the compounds *rac*-**20g** and *rac*-**20g**′ are inseparable the mixture was then treated with TESOTf-2,6-lutidine in CH_2Cl_2 (0 °C to room temperature, 1 h) to convert *rac*-**20g**′ into the corresponding TES ether *rac*-**20g**″ (90% yield) for column chromatographic separation over silica gel (Scheme 6). We found that the *trans*:*cis* ratio for *rac*-**20g** changed



Scheme 6. Silylation of the mixture of **20g** and **20g**′ for separation.

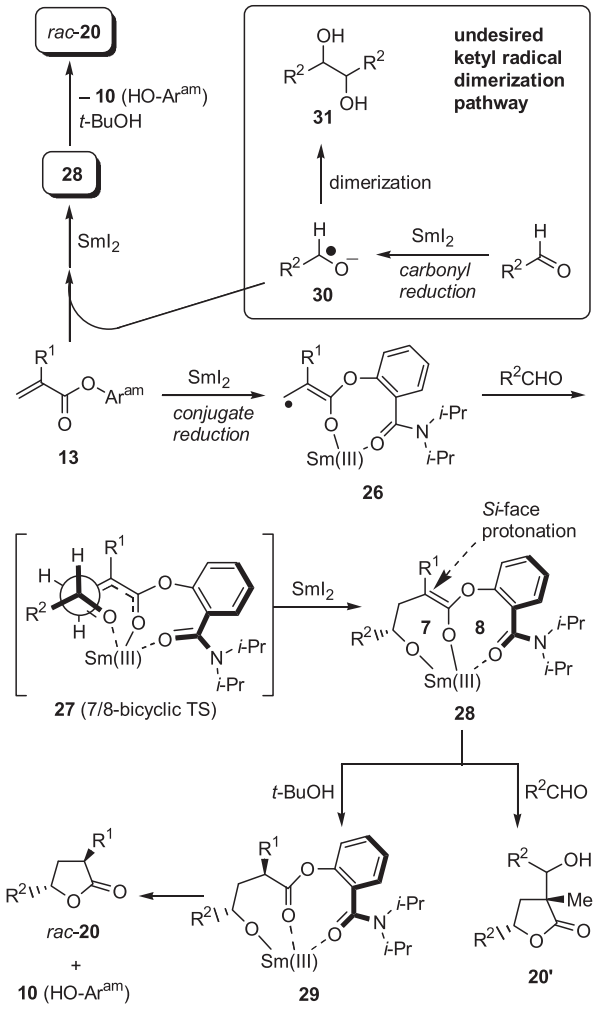
from the original 98:2 to 84:16, indicating that partial epimerization occurred under the silylation conditions. Nevertheless, it is pleased to find the excellent *trans*:*cis* ratio of 98:2 for *rac*-**20g** and a single diastereomer for *rac*-**20g**′. Therefore, the lack of the dimer byproducts in the reaction of **13a** suggests it is a superior substrate favored for conjugate reduction by SmI_2 as compared to the simple methacrylates **3**.[1m,7,9]

In order to confirm the assigned stereochemistry for the *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones *rac*-**20**, an alternative synthesis of *trans* isomer *rac*-**20a** was carried out (Scheme 7). The SmI_2-mediated reductive coupling of methyl acrylate (**21**) with trimethylacetaldehyde gave the dihydrofuran-2(3*H*)-one *rac*-**22** in 50% isolated yield. Methylation of *rac*-**22** afforded the *trans* product *rac*-**20a** in 80% yield and in almost a single diastereoisomer.[13] Treatment of *rac*-**20a** with LDA and protonation of the resultant enolate with 2,6-di-*tert*-butylphenol (**23**), as a bulky proton source, at −78 °C to furnish the *cis* isomer *rac*-**24** in 80% yield and in a dr value of >98:2. Therefore, the assigned *trans* stereochemistry of *rac*-**20a** was confirmed unambiguously by comparison of its ^{1}H and ^{13}C NMR spectral data with those of the authentic sample. In a similar manner, treatment of *rac*-**4b** of *trans*:*cis* ratio of 96:4 with LDA followed by protonation with **23** afforded the *cis* isomer *rac*-**25** in 86% yield as a 15:85 mixture in favor of the *cis*-isomer.



Scheme 7. Alternative synthesis of *rac*-**20a**, *rac*-**24** and *rac*-**25**.

We propose mechanisms for the SmI_2-mediated reductive coupling of 2-alkylacrylates **13** with aldehydes as illustrated in Scheme 8. Reduction of an aldehyde (via carbonyl reduction) and the 2-alkylacrylate **13** (via conjugate reduction) should form the ketyl radical **30** and the radical enolate **26**, respectively. In view of the primary radical nature of the radical enolate, carbonyl reduction of an aldehyde might compete with conjugate reduction as in the case of the simple alkyl methacrylates **3**. Dimerization of the ketyl radical **30** could become a significant side reaction for α-non-branched aldehydes (entry 8, Table 1). Addition of the radical enolate **26** with an aldehyde is considered to involve a 7/8-bicyclic transition state **27**, after picking up an electron from SmI_2, leading to the γ-alkoxide-bound Sm(III) enolate **28** where the amide carbonyl oxygen atom is also coordinated to Sm(III) to form another eight-membered ring. Alternatively, the same Sm(III) enolate **28** could be formed from 1,4-addition of the ketyl radical **30** with **13** via a similar 7/8-bicyclic transition state **27**. Since the amide moiety blocks the *Re*-face of the enolate **28** (assuming R^1 has the least priority), its protonation should be favored from the *Si*-face, resulting in the *anti*-relationship for R^1 and R^2 in **29**. Finally, lactonization of **29** with cleavage of the 2-hydroxybenzamide **10**

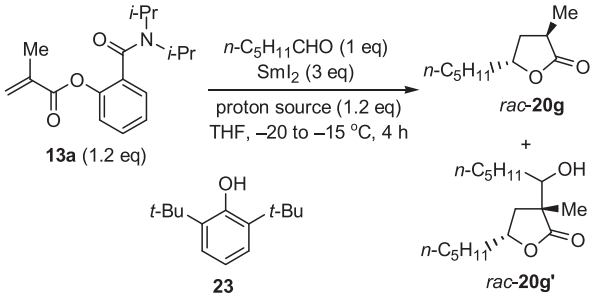


Scheme 8. Proposed mechanisms for the reactions of 13 with aldehydes.

affords the *trans* end product *rac*-**20** in high diastereoselectivity. Therefore, it can be concluded that high diastereoselectivity in the SmI_2-mediated reductive coupling reactions of aliphatic aldehydes could be achieved by using 2-alkylacrylates **13** derived from the 2-amido arenol **10** via chelation of the amide carbonyl oxygen atom within the Sm(III) enolate intermediate. As a minor reaction pathway, the Sm(III) enolate **28** was found to undergo an aldol reaction with linear aliphatic aldehydes to form **20′** as a single diastereomer. The stereochemistry of **20′** is tentatively proposed according to the stereochemical result of the protonation of **28**.

Formation of the aldol byproducts such as **20e′** and **20g′** has not been reported in the literature. We considered that the coordination of the amido moiety in the Sm(III) enolate **28** as given in Scheme 8 enhanced its stability and then the aldol side reaction could compete with the protonation pathway. We envisioned that the proton source should have an effect on the product distribution and the reaction of **13a** with *n*-hexanal in the presence of different proton sources was performed and the results are summarized in Table 2. Freshly distilled *t*-BuOH or replacement of *t*-BuOH by *i*-PrOH has no significant effect on the product ratio (entries 1–3, Table 2). However, use of much more acidic proton donors such as 2,6-di-*tert*-butylphenol (**23**) and $MeSO_2NH_2$ could suppress formation of the aldol byproduct *rac*-**20g′** (entries 4 and 5, Table 2). With a higher product ratio in the reaction of entry 5 of Table 2, it became possible to isolate a pure sample of the product *rac*-**20g** with a 98:2 ratio for the *trans* and *cis* isomers.

Table 2
Effect of proton source on SmI2-mediated reductive coupling of **13a**



Entry	Protone source	*rac*-20g (%)[a,b]	*rac*-20g′ (%)[a,c]	Ratio[d]
1[e]	*t*-BuOH	40	30	57:43
2	*t*-BuOH[f]	52	27	66:34
3	*i*-PrOH	48	24	67:33
4	**23**	50	9	85:15
5	$MeSO_2NH_2$	52	7	88:12

[a] Yields calculated based on the ^1H NMR spectrum of the isolated product mixture.
[b] The *trans*:*cis* ratio is 98:2 in all entries.
[c] A single diastereomer was observed in the ^1H NMR spectrum.
[d] The ratio of *rac*-**20g** to *rac*-**20g′**.
[e] Data taken from the entry 10 of Table 1.
[f] Freshly distilled.

It should be mentioned that the synthesized *trans* and *cis* compounds *rac*-**20a** and *rac*-**24** are the useful starting materials for construction of the building blocks for naturally occurring enamide-containing macrolides, (−)-palmyrolide A (**30**),[14,15] laingolide (**31**),[16] laingolide A (**32**),[17,18] and madangolide (**33**)[17] (Fig. 1). We have completed diverted total synthesis of palmyrolide A and laingolide A, and their stereoisomers via multimodule assembly strategy based on the key structural modules derived from *rac*-**20a** and *rac*-**24** and the results will be disclosed elsewhere.[19]

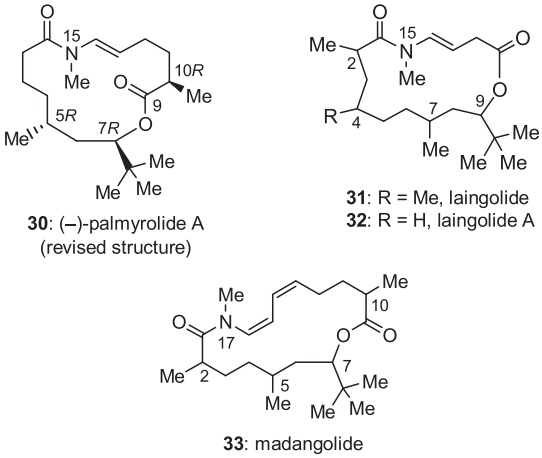


Fig. 1. Structures of the macrolides possessing a 1,3-Me/*t*-Bu subunit.

3. Conclusion

In summary, we have developed a practically useful protocol for SmI_2-mediated reductive coupling reactions of aliphatic aldehydes with substituted acrylates derived from the 2-amido arenols (HO-Ar^{am}) such as the crotonate **11** and the 2-alkylacrylates **13a**–**c**. These novel α,β-unsaturated esters undergo preferential conjugate reduction than aldehyde carbonyl reduction so that the

dimerization of α-non-branched aldehydes could be suppressed, leading to high yields for the desired dihydrofuran-2(3*H*)-ones. Moreover, coordination of the amide group within the Sm(III) enolate **28** forms the 7/8-bicyclic architecture, which enables high diastereoselective protonation to furnish *trans*-3,5-disubstituted dihydrofuran-2(3*H*)-ones in diastereoselectivity ranging from 90:10 to 98:2 regardless the structures of the aliphatic aldehydes. It is found that an aldol reaction of the Sm(III) enolate **28** competes with protonation in the reactions of α-non-branched aldehydes. Future effort would be directed to searching for conditions favorable for protonation of the Sm(III) enolate **28**. Therefore, the desired dihydrofuran-2(3*H*)-ones could be prepared in high yields even in the case of α-non-branched aldehydes.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively). Residual solvent peaks are used as the internal reference; the signals at 7.26 and 77.16 ppm are set for ^{1}H and ^{13}C NMR spectra, respectively, taken in $CDCl_3$ while the signals at 2.50 and 40.45 ppm are set for ^{1}H and ^{13}C NMR spectra, respectively, taken in DMSO-d_6. IR spectra were taken on an FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured by TOF MS under the +CI or −CI conditions. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received unless otherwise mentioned.

4.2. *N,N*-Diisopropyl 2-hydroxybenzamide (10)

To the solid salicylic acid (**9**, 2.00 g, 14.48 mmol) in a dry round bottom flask, the freshly distilled $SOCl_2$ (23.0 mL, 317 mmol) was added dropwise. The resultant mixture was heated under refluxing at 80 °C for 4 h and then the excess $SOCl_2$ was removed through distillation under reduced pressure to give the corresponding acyl chloride, which was used for the next step without further purification.

To a solution of freshly distilled $(i\text{-Pr})_2NH$ (10.15 mL, 72.40 mmol) in dry PhMe (145 mL) cooled in an ice−water bath (0 °C) was added dropwise the acyl chloride prepared above. After heating at 80 °C for 10 h, the reaction was quenched with aqueous HCl (1.0 M, 5 mL) and the reaction mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 9.1% EtOAc in hexane) to give **10** (2.72 g, 85% for 2 steps) as a white solid. Mp 154−155 °C (CH_2Cl_2−hexane); R_f=0.30 (16.7% EtOAc in hexane); IR (film): 3153 (br), 2970, 1591, 1447, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 7.21 (ddd, *J*=8.2, 7.6, 1.6 Hz, 1H), 7.12 (dd, *J*=7.6, 1.2 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 6.79 (dd, *J*=8.0, 7.6 Hz, 1H), 3.86 (br s, 2H), 1.35 (d, *J*=6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 157.0, 131.2, 126.7, 121.5, 118.7, 117.7, 48.8 (br, ×2), 20.9 (×4); HRMS (+CI) calcd for $C_{13}H_{20}NO_2$ 222.1494 (M+H$^+$), found 222.1494.

4.3. (*E*)-2-(*N,N*-Diisopropylcarbamoyl)phenyl but-2-enoate (11)

To a solution of **10** (200.0 mg, 0.99 mmol), DMAP (12.0 mg, 0.1 mmol), and Et_3N (0.28 mL, 2.0 mmol) in dry PhMe (10 mL) cooled in an ice−water bath (0 °C) was added dropwise crotonoyl chloride (0.19 mL, 2.0 mmol). The resultant mixture was heated at 70 °C for 12 h and the reaction mixture was then quenched with aqueous HCl (1.0 M, 2 mL). The reaction mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (16.7% EtOAc in hexane) to give **11** (225.0 mg, 86%) as a colorless oil. R_f=0.20 (16.7% EtOAc in hexane); IR (film): 2969, 1737, 1635, 1440, 1341, 1207, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.10 (m, 5H), 5.98 (d, *J*=15.2 Hz, 1H), 3.74−3.69 (m, 1H), 3.40−3.41 (m, 1H), 1.91 (d, *J*=6.4 Hz, 3H), 1.52 (d, *J*=6.4 Hz, 3H), 1.44 (d, *J*=6.4 Hz, 3H), 1.05 (d, *J*=5.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 164.3, 147.7, 146.5, 131.8, 129.3, 126.4, 125.9, 123.1, 121.6, 50.9, 45.8, 20.9, 20.6, 20.5, 20.4, 18.3; HRMS (+CI) calcd for $C_{17}H_{24}NO_3$ 290.1756 (M+H$^+$), found 290.1761.

4.4. 2-(*N,N*-Diisopropylcarbamoyl)phenyl methacrylate (13a)

To a solution of **10** (2.72 g, 12.3 mmol), DMAP (151.0 mg, 1.23 mmol), and Et_3N (3.45 mL, 24.6 mmol) in dry CH_2Cl_2 (123 mL) cooled in an ice−water bath (0 °C) was added dropwise methacryloyl chloride (2.53 mL, 24.6 mmol). The resultant reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for another 5 h. The reaction was quenched with aqueous HCl (1.0 M, 3 mL) and the reaction mixture was extracted with CH_2Cl_2 (100 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 16.7% EtOAc in hexane) to give **13a** (3.38 g, 95%) as a colorless oil. R_f=0.33 (16.7% EtOAc in hexane); IR (film): 2969, 1738, 1636, 1439, 1340, 1207, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 1H), 7.21−7.15 (m, 3H), 6.31 (s, 1H), 5.72−5.68 (m, 1H), 3.70 (septet, *J*=6.8 Hz, 1H), 3.42 (septet, *J*=6.8 Hz, 1H), 1.99 (s, 3H), 1.49 (d, *J*=6.8 Hz, 3H), 1.42 (d, *J*=6.8 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.4, 146.6, 135.4, 131.7, 129.2, 127.7, 126.3, 125.8, 123.1, 50.8, 45.8, 20.8, 20.4, 20.4, 20.4, 18.2; HRMS (+CI) calcd for $C_{17}H_{24}NO_3$ 290.1756 (M+H$^+$), found 290.1753.

4.5. 2-(*N,N*-Diisopropylcarbamoyl)phenyl 2-methylenebutanoate (13b)

A solution of **10** (300.0 mg, 1.36 mmol), 2-methylenebutanoic acid[12] (**15**, 272.0 mg, 2.72 mmol), DMAP (16.6 mg, 0.14 mmol), and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI, 782.0 mg, 4.08 mmol) in dry PhMe (14 mL) was heated at 80 °C with stirring for 9 h. The reaction was quenched by water and the reaction mixture was extracted with EtOAc (10 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 16.7% EtOAc in hexane) to give **13b** (396.0 mg, 96%) as a colorless oil. R_f=0.28 (16.7% EtOAc in hexane); IR (film): 2969, 1736, 1636, 1439, 1340, 1207, 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 1H), 7.22−7.18 (m, 3H), 6.37 (d, *J*=0.4 Hz, 1H), 5.70 (d, *J*=1.2 Hz, 1H), 3.73 (septet, *J*=6.8 Hz, 1H), 3.43 (septet, *J*=6.8 Hz, 1H), 2.39 (q, *J*=7.2 Hz, 2H), 1.51 (d, *J*=6.8 Hz, 3H), 1.43 (d, *J*=6.8 Hz, 3H), 1.11 (t, *J*=7.2 Hz, 3H), 1.06 (d, *J*=6.8 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.4, 146.8, 141.4, 131.9, 129.3, 126.4, 126.0, 125.9, 123.2, 50.9, 45.9, 24.8, 20.9, 20.5 (×2), 20.5, 12.7; HRMS (+CI) calcd for $C_{18}H_{26}NO_3$ 304.1913 (M+H$^+$), found 304.1917.

4.6. 2-(*N*,*N*-Diisopropylcarbamoyl)phenyl 2-methylene-3-phenylpropionate (13c)

A solution of **10** (1.00 g, 4.52 mmol), 2-methylene-3-phenylpropionic acid (**19**, 1.47 g, 9.04 mmol), DMAP (55.0 mg, 0.45 mmol), and EDCI (2.60 g, 13.5 mmol) in dry PhMe (45 mL) was heated at 80 °C with stirring for 9 h and quenched with water. The reaction was quenched by water and the reaction mixture was extracted with EtOAc (50 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 16.7% EtOAc in hexane) to give **13c** (1.57 g, 95%) as a colorless oil. R_f=0.40 (25% EtOAc in hexane); IR (film): 2969, 1737, 1635, 1439, 1341, 1206, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.20 (m, 8H), 7.14 (d, *J*=8.0 Hz, 1H), 6.49 (s, 1H), 5.64 (d, *J*=0.8 Hz, 1H), 3.76–3.66 (m, 3H), 3.44 (septet, *J*=6.8 Hz, 1H), 1.53 (d, *J*=6.8 Hz, 3H), 1.44 (d, *J*=6.8 Hz, 3H), 1.06 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.0, 146.7, 139.5, 138.3, 131.7, 129.4, 129.3 (×2), 128.6 (×2), 128.5, 126.5, 126.4, 125.9, 123.2, 50.9, 45.9, 38.1, 20.9, 20.5, 20.4, 20.34; HRMS (+CI) calcd for $C_{23}H_{28}NO_3$ 366.2069 ($M+H^+$), found 366.2073.

4.7. 2-Methylenebutanoic acid (15)[12]

To a solution of 2-ethylmalonic acid (**14**, 1.50 g, 11.35 mmol) in EtOAc (114 mL) cooled in an ice–water bath (0 °C) was added dropwise Et_2NH (1.76 mL, 17.01 mmol) followed by addition of solid paraformaldehyde (682.0 mg, 22.70 mmol). The resultant mixture was stirred under refluxing for 4 h. The reaction was quenched with water and the reaction mixture was adjusted to ca. pH 1 with concn. aqueous HCl. The resultant mixture was extracted with EtOAc (100 mL×3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexane) to give **15**[12] (1.08 g, 95%) as a yellow oil. R_f=0.60 (25% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 11.98 (br s, 1H), 6.25 (s, 1H), 5.61 (d, *J*=2.0 Hz, 1H), 2.29 (qd, *J*=7.6, 0.8 Hz, 2H), 1.06 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 141.8, 125.9, 24.4, 12.6; HRMS (+CI) calcd for $C_5H_9O_2$ 101.0603 ($M+H^+$), found 101.0607.

4.8. 2-Methylene-3-phenylpropionic acid (19)

A solution of diethyl malonate (**16**) (200.0 mg, 1.25 mmol), K_2CO_3 (345.0 mg, 2.50 mmol), tetrabutylammonium iodide (23.0 mg, 0.06 mmol), and benzyl bromide (178 μL, 1.50 mmol) in MeCN (13 mL) was stirred under refluxing for 10 h. The reaction was quenched with aqueous 10% HCl and the reaction mixture was extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a crude product of **17**.[20]

To a suspension of the above crude **17** in water (10 mL) was added solid NaOH (100.0 mg, 2.50 mmol) followed by refluxing with stirring for 5 h. The reaction mixture was adjusted to ca. pH 1 with concn. aqueous HCl and was then extracted with EtOAc (20 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexane) to give 2-benzylmalonic acid (**18**, 187.0 mg, 93% for 2 steps) as a yellow oil. R_f=0.30 (50% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 7.30–7.18 (m, 5H), 3.56 (t, *J*=7.6 Hz, 1H), 3.04 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 138.8, 128.9 (×2), 128.4 (×2), 126.5, 53.4, 34.4.

To a solution of 2-benzylmalonic acid (**18**, 3.50 g, 17.9 mmol) in EtOAc (180 mL) cooled in an ice–water bath (0 °C) was added dropwise Et_2NH (2.77 mL, 26.8 mmol) followed by addition of solid paraformaldehyde (1.07 g, 35.8 mmol). The resultant mixture was stirred under refluxing for 3 h. The reaction was quenched with water and the reaction mixture was adjusted to ca. pH 1 with concn. aqueous HCl. The resultant mixture was extracted with EtOAc (200 mL×3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexane) to give **19** (2.63 g, 90%) as a yellow oil. R_f=0.62 (50% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 12.17 (br s, 1H), 7.44–7.39 (m, 2H), 7.35–7.31 (m, 3H), 6.51 (d, *J*=0.8 Hz, 1H), 5.68 (d, *J*=1.6 Hz, 1H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 139.7, 138.5, 129.1 (×2), 128.8, 128.6 (×2), 126.5, 37.6; HRMS (+CI) calcd for $C_{10}H_{10}O_2$ 162.0681 (M^+), found 162.0683.

4.9. General procedure for SmI_2-mediated reductive coupling of crotonates/acrylates with aldehydes

To a solution of SmI_2 in dry THF (0.1 M in THF, 110 mL, 11.0 mmol, 3 equiv) cooled at −20 °C under an argon atmosphere was added a solution of the methacrylate **13a** (1.27 g, 4.38 mmol, 1.2 equiv), *t*-BuOH (0.42 mL, 4.38 mmol, 1.2 equiv), and trimethylacetaldehyde (0.40 mL, 3.65 mmol, 1 equiv) in THF (10 mL, degassed by argon). The mixture was stirred at −20 and −15 °C for 4 h and quenched with aqueous HCl (1.0 M, 10 mL). The reaction mixture was condensed under reduced pressure by removing THF and then extracted with EtOAc (30 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 6.3% EtOAc in hexane) to give **20a** (541.7 mg, 95%; entry 2, Table 1).

*4.9.1. cis-4-Methyl-5-pentyldihydrofuran-2(3H)-one (rac-**2a**) and dodecane-6,7-diol (**12a**).* Prepared from ethyl crotonate (**1**) and hexanal in 41% yield as an 84:16 mixture of *cis* and *trans* isomers. The dimer **12a** of the aldehyde was also isolated in 34% yield as an 81:19 mixture of two diastereomers. Compound *rac*-**2a**: a pale-yellow oil; R_f=0.45 (25% EtOAc in hexane); IR (film): 2956, 2934, 1776, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; for the major isomer) δ 4.43–4.38 (m, 1H), 2.66 (dd, *J*=17.2, 8.0 Hz, 1H), 2.60–2.50 (m, 1H), 2.16 (dd, *J*=17.2, 4.0 Hz, 1H), 1.65–1.56 (m, 1H), 1.49–1.42 (m, 2H), 1.38–1.21 (m, 5H), 0.98 (d, *J*=7.2 Hz, 3H), 0.86 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; for the major isomer) δ 177.1, 83.8, 37.6, 33.1, 31.7, 29.9, 25.6, 22.5, 14.0, 13.9; HRMS (−CI) calcd for $C_{10}H_{17}O_2$ 169.1229 ($M-H^+$), found 169.1226.

Compound **12a**: a pale-yellow oil; R_f=0.31 (25% EtOAc in hexane); IR (film): 3308 (br), 2919, 2854, 1467, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (t, *J*=5.2 Hz, 0.38H for the minor isomer), 3.39 (d, *J*=6.0 Hz, 1.62H for the major isomer), 2.64 (br s, 2H), 1.52–1.20 (m, 8H), 0.86 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; for the major isomer) δ 74.7 (×2), 33.7 (×2), 32.0 (×2), 25.5 (×2), 22.7 (×2), 14.2 (×2); HRMS (−CI) calcd for $C_{12}H_{25}O_2$ 201.1855 ($M-H^+$), found 201.1847.

*4.9.2. cis-5-[2-(((tert-Butyldiphenyl)silyl)oxy)]-ethyl-4-methyldihydrofuran-2(3H)-one (rac-**2c**).* Prepared from the crotonate **11** and $TBDPSOCH_2CH_2CHO$ in 74% yield as an 89:11 mixture of *cis* and *trans* isomers. Compound *rac*-**2c**: a pale-yellow oil; R_f=0.62 (25% EtOAc in hexane); IR (film): 2960, 2930, 2857, 1780, 1428, 1165, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; for the major isomer) δ 7.68–7.65 (m, 4H), 7.46–7.37 (m, 6H), 4.75–4.69 (m, 1H), 3.88–3.79 (m, 2H), 2.71 (dd, *J*=17.2, 8.0 Hz, 1H), 2.62–2.53 (m, 1H), 2.18 (dd, *J*=16.8, 3.6 Hz, 1H), 1.85–1.79 (m, 2H), 1.07 (s, 9H), 1.00 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; for the major isomer) δ 176.9, 135.6 (×2), 135.6 (×2), 133.7, 133.5, 129.9 (×2), 127.9 (×4),

80.3, 60.5, 37.6, 33.1, 33.0, 27.0 (×3), 19.3, 14.2; HRMS (+CI) calcd for $C_{23}H_{30}O_3Si$ 382.1964 (M^+), found 382.1941.

*4.9.3. cis-5-[2-((4-Methoxybenzyl)oxy)]ethyl-4-methyldihydrofuran-2(3H)-one (rac-**2d**).* Prepared from the crotonate **11** and $PMBOCH_2CH_2CHO$ in 75% yield as an 87:13 mixture of *cis* and *trans* isomers. Compound *rac*-**2d**: a pale-yellow oil; R_f=0.20 (25% EtOAc in hexane); IR (film): 2964, 2870, 1775, 1613, 1514, 1248, 1170, 1093, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; for the major isomer) δ 7.25 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.68–4.63 (m, 1H), 4.46 and 4.42 (ABq, J=11.6 Hz, 2H), 3.79 (s, 3H), 3.63–3.56 (m, 2H), 2.69 (dd, J=17.2, 8.0 Hz, 1H), 2.61–2.54 (m, 1H), 2.18 (dd, J=17.2, 4.0 Hz, 1H), 1.88–1.82 (m, 2H), 1.00 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; for the major isomer) δ 176.9, 159.3, 130.3, 129.4 (×2), 113.9 (×2), 80.5, 73.0, 66.5, 55.3, 37.5, 33.0, 30.6, 14.1; HRMS (+CI) calcd for $C_{15}H_{20}O_4$ 264.1357 (M^+), found 264.1357.

*4.9.4. cis-5-Cyclopropyl-4-methyldihydrofuran-2(3H)-one (rac-**2e**).*[6] Prepared from the crotonate **11** and cyclopropanecarboxaldehyde in 85% yield as a 95:5 mixture of *cis* and *trans* isomers. Compound *rac*-**2e**: a pale-yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (dd, J=9.2, 6.4 Hz, 1H), 2.69–2.62 (m, 2H), 2.30–2.22 (m, 1H), 1.17 (d, J=7.2 Hz, 3H), 1.02–0.94 (m, 1H), 0.72–0.59 (m, 2H), 0.47–0.41 (m, 1H), 0.29–0.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 88.8, 37.2, 33.7, 14.9, 10.4, 3.7, 1.9.

*4.9.5. trans-5-(2-Phenylethyl)-3-methyldihydro-furan-2(3H)-one (rac-**4b**) and 1,6-diphenylhexane-3,4-diol (**12b**).* Prepared from methyl methacrylate (**3**: X=OMe) and $PhCH_2CH_2CHO$ in 27% yield as a 74:26 mixture of *trans* and *cis* isomers along with 30% yield of the aldehyde dimer **12b** as a 74:26 mixture of diastereomers (entry 8, Table 1). The compound *rac*-**4b** was also obtained in 30–37% yields and in a 96:4 ratio of *trans*:*cis* isomers from the reaction of **13a** with $PhCH_2CH_2CHO$ (entry 9, Table 1). Compound *rac*-**4b**: a pale-yellow oil; R_f=0.32 (16.7% EtOAc in hexane); IR (film): 2936, 1770, 1455, 1186, 1161, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H), 4.53–4.46 (m, 1H), 2.86–2.65 (m, 3H), 2.15–2.08 (m, 1H), 2.05–1.96 (m, 2H), 1.90–1.81 (m, 1H), 1.28 (d, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 140.9, 128.7 (×2), 128.6 (×2), 126.3, 77.5, 37.4, 35.5, 34.1, 31.8, 16.0; HRMS (+CI) calcd for $C_{13}H_{17}O_2$ 205.1229 ($M+H^+$), found 205.1237.

Compound **12b**: a pale-yellow oil; R_f=0.17 (25% EtOAc in hexane); IR (film): 3385 (br), 2943, 1496, 1455, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 10H), 3.63–3.60 (m, 0.52H), 3.48–3.44 (m, 1.48H), 2.90–2.78 (m, 2H), 2.72–2.60 (m, 2H), 2.20–1.85 (br s, 2H), 1.83–1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$; for the major isomer) δ 141.9 (×2), 128.6 (×4), 128.6 (×4), 126.1 (×2), 74.0 (×2), 35.4 (×2), 32.0 (×2); HRMS (+CI) calcd for $C_{18}H_{23}O_2$ 271.1698 ($M+H^+$), found 271.1695.

*4.9.6. trans-5-tert-Butyl-3-methyldihydrofuran-2(3H)-one (rac-**20a**).* Prepared from the methacrylate **13a** and trimethylacetaldehyde in 95% yield as a 98:2 mixture of *trans* and *cis* isomers (entry 2, Table 1). Compound *rac*-**20a**: a pale-yellow oil; R_f=0.33 (16.7% EtOAc in hexane); IR (film): 2966, 1772, 1479, 1368, 1189, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, J=7.6, 6.4 Hz, 1H), 2.64–2.58 (m, 1H), 2.19 (ddd, J=13.2, 9.6, 6.4 Hz, 1H), 1.77 (ddd, J=13.6, 8.0, 6.0 Hz, 1H), 1.23 (d, J=7.6 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 85.9, 35.0, 34.2, 30.6, 24.9 (×3), 16.7; HRMS (+CI) calcd for $C_9H_{17}O_2$ 157.1229 ($M+H^+$), found 157.1234.

*4.9.7. trans-5-tert-Butyl-3-ethyldihydrofuran-2(3H)-one (rac-**20b**).* Prepared from the 2-ethylacrylate **13b** and trimethylacetaldehyde in 82% yield as a 95:5 mixture of *trans* and *cis* isomers (entry 3, Table 1). Compound *rac*-**20b**: a pale-yellow oil; R_f=0.50 (16.7% EtOAc in hexane); IR (film): 2964, 1771, 1184, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, J=7.6, 6.8 Hz, 1H), 2.52–2.47 (m, 1H), 2.15 (ddd, J=13.6, 10.0, 6.8 Hz, 1H), 1.86 (ddd, J=13.6, 8.4, 5.6 Hz, 1H), 1.85–1.76 (m, 1H), 1.57–1.51 (m, 1H), 1.00 (t, J=7.6 Hz, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 86.3, 41.8, 34.3, 28.2, 25.0 (×3), 24.7, 11.8; HRMS (+CI) calcd for $C_{10}H_{19}O_2$ 171.1385 ($M+H^+$), found 171.1385.

*4.9.8. trans-3-Benzyl-5-tert-butyldihydrofuran-2(3H)-one (rac-**20c**).* Prepared from the 2-benzylacrylate **13c** and trimethylacetaldehyde in 86% yield as a 90:10 mixture of *trans* and *cis* isomers (entry 4, Table 1). Compound *rac*-**20c**: a pale-yellow oil; R_f=0.58 (25% EtOAc in hexane); IR (film): 2961, 1769, 1177, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H), 4.00 (dd, J=8.0, 6.8 Hz, 1H), 3.17 (dd, J=13.6, 4.0 Hz, 1H), 2.93–2.88 (m, 1H), 2.78 (dd, J=13.6, 9.6 Hz, 1H), 2.04 (ddd, J=13.6, 9.6, 6.4 Hz, 1H), 1.91 (ddd, J=14.0, 8.0, 5.6 Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 138.4, 129.0 (×2), 128.8 (×2), 126.9, 86.3, 42.0, 37.1, 34.3, 27.6, 25.0 (×3); HRMS (−CI) calcd for $C_{15}H_{19}O_2$ 231.1385 ($M-H^+$), found 231.1389.

*4.9.9. trans-5-Cyclohexyl-3-methyldihydrofuran-2(3H)-one (rac-**20d**).* Prepared from the methacrylate **13a** and cyclohexanecarboxaldehyde in 80% yield as a 97:3 mixture of *trans* and *cis* isomers (entry 5, Table 1). Compound *rac*-**20d**: a pale-yellow oil; R_f=0.50 (16.7% EtOAc in hexane); IR (film): 2928, 1770, 1451, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24–4.19 (m, 1H), 2.69–2.59 (m, 1H), 2.19 (ddd, J=13.2, 9.2, 5.6 Hz, 1H), 1.93–1.86 (m, 2H), 1.78–1.73 (m, 2H), 1.69–1.61 (m, 2H), 1.52–1.42 (m, 1H), 1.26 (d, J=7.6 Hz, 3H), 1.25–1.10 (m, 3H), 1.05–0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 82.5, 42.4, 34.3, 33.0, 28.7, 28.0, 26.2, 25.7, 25.5, 16.2; HRMS (+CI) calcd for $C_{11}H_{19}O_2$ 183.1385 ($M+H^+$), found 183.1386.

*4.9.10. trans-5-Cyclohexyl-3-ethyldihydrofuran-2(3H)-one (rac-**20e**) and the aldol byproduct rac-**20e′**.* Prepared from the 2-ethylacrylate **13b** and cyclohexanecarboxaldehyde in 87% yield as a 95:5 mixture of *trans* and *cis* isomers along with 6% of the aldol byproduct *rac*-**20e′** (entry 6, Table 1). Compound *rac*-**20e**: a pale-yellow oil; R_f=0.53 (16.7% EtOAc in hexane); IR (film): 2929, 1769, 1451, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20–4.14 (m, 1H), 2.51–2.43 (m, 1H), 2.10 (ddd, J=13.2, 9.2, 6.0 Hz, 1H), 1.97–1.69 (m, 5H), 1.68–1.57 (m, 2H), 1.55–1.39 (m, 2H), 1.26–1.08 (m, 3H), 1.04–0.60 (m, 2H), 0.97 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 82.9, 42.7, 41.1, 30.7, 28.7, 28.1, 26.3, 25.7, 25.6, 24.3, 11.7; HRMS (+CI) calcd for $C_{12}H_{21}O_2$ 197.1542 ($M+H^+$), found 197.1543.

Compound *rac*-**20e′**: a pale-yellow oil; R_f=0.48 (16.7% EtOAc in hexane); IR (film): 3489 (br), 2925, 2852, 1747, 1449, 1200, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09–4.03 (m, 1H), 3.84 (br s, 1H), 2.38 (dd, J=12.8, 10.0 Hz, 1H), 2.06–1.96 (m, 2H), 1.87 (dd, J=12.4, 6.8 Hz, 1H), 1.82–1.37 (m, 15H), 1.32–1.09 (m, 6H), 1.06–0.95 (m, 2H), 0.96 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 82.4, 76.3, 54.1, 43.4, 39.0, 32.9, 31.4, 29.3, 28.2, 27.9, 26.8, 26.5, 26.4, 26.2, 25.9, 25.8, 25.6, 9.2; HRMS (+CI) calcd for $C_{19}H_{33}O_3$ 309.2430 ($M+H^+$), found 309.2443.

*4.9.11. trans-3-Benzyl-5-cyclohexyldihydrofuran-2(3H)-one (rac-**20f**).* Prepared from the 2-benzylacrylate **13c** and cyclohexanecarboxaldehyde in 99% yield as a 92:8 mixture of *trans* and *cis* isomers (entry 7, Table 1). Compound *rac*-**20f**: a pale-yellow oil; R_f=0.52 (16.7% EtOAc in hexane); IR (film): 2926, 1767, 1452, 1166, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 4.07–4.01 (m, 1H), 3.18 (dd, J=13.6, 4.4 Hz, 1H), 2.94–2.85 (m, 1H), 2.76 (dd, J=13.6, 9.2 Hz, 1H), 2.01 (dd, J=8.0, 7.2 Hz, 2H), 1.90–1.82 (m, 1H), 1.78–1.54 (m, 4H), 1.49–1.38 (m, 1H), 1.25–1.10 (m, 3H), 1.02–0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 138.4, 129.0 (×2), 128.7

(×2), 126.8, 82.9, 42.5, 41.4, 36.8, 30.2, 28.6, 28.0, 26.2, 25.6, 25.5; HRMS (+CI) calcd for $C_{17}H_{23}O_2$ 259.1698 ($M+H^+$), found 259.1696.

*4.9.12. trans-3-Methyl-5-n-pentyldihydrofuran-2(3H)-one (rac-**20g**) and the aldol byproduct rac-**20g**″.* Prepared from the methacrylate **13a** and *n*-hexanal in 40% yield as a 98:2 mixture of *trans* and *cis* isomers along with the aldol byproduct *rac*-**20g**′ in 30% yield as estimated by ^{1}H NMR analysis of the inseparable mixture (entry 10, Table 1). The chemical shifts for C5–H are assigned as follows: 4.50–4.44 for the major *trans* isomer of *rac*-**20g**, 4.43–4.26 for *rac*-**20g**′, and 4.33–4.28 for the minor *cis* isomer of *rac*-**20g**, respectively. The inseparable mixture of *rac*-**20g** and *rac*-**20g**′ was silylated (TESOTf-2,6-lutidine, CH_2Cl_2, 0 °C to rt, 1 h, 90%) to form the TES ether *rac*-**20g**″ and the recovered *rac*-**20g**. The latter was found to undergo partial epimerization to give an 84:16 mixture of *trans* and *cis* isomers. Compound *rac*-**20g** (*trans*:*cis*=84:16): a pale-yellow oil; R_f=0.60 (25% EtOAc in hexane); IR (film): 2934, 1772, 1458, 1190, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51–4.44 (m, 0.84H), 4.33–4.28 (m, 0.16H), 2.70–2.62 (m, 0.84H), 2.49–2.42 (m, 0.16H), 2.12–2.05 (m, 1H), 2.01–1.93 (m, 1H), 1.72–1.21 (m, 11H), 0.87 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ for the major isomer, 180.3, 78.6, 35.5, 35.5, 34.1, 31.6, 25.1, 22.6, 16.0, 14.0 and for the minor isomer, 179.8, 78.8, 37.5, 36.0, 35.6, 31.6, 25.0, 22.6, 16.0, 15.2; HRMS (–CI) calcd for $C_{10}H_{17}O_2$ 169.1229 ($M-H^+$), found 169.1230.

A sample of *rac*-**20g** with a *trans*:*cis* ratio of 98:2 was obtained from the reaction of **13a** with *n*-hexanal in the presence of $MeSO_2NH_2$ as the proton source (see entry 5, Table 2).

Compound *rac*-**20g**″: a pale-yellow oil; R_f=0.80 (25% EtOAc in hexane); IR (film): 2956, 2936, 1771, 1459, 1202, 1123, 1094, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39–4.32 (m, 1H), 3.95–3.92 (m, 1H), 2.27 (dd, J=12.4, 10.8 Hz, 1H), 1.78 (dd, J=12.4, 6.4 Hz, 1H), 1.73–1.66 (m, 1H), 1.60–1.20 (m, 15H), 1.12 (s, 3H), 0.97–0.85 (m, 15H), 0.65–0.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 77.6, 74.6, 51.0, 35.8, 35.3, 33.0, 32.3, 31.7, 25.6, 25.1, 22.7, 22.6, 20.6, 14.2, 14.1, 7.1 (×3), 5.3 (×3); HRMS (–CI) calcd for $C_{22}H_{43}O_3Si$ 383.2981 ($M-H^+$), found 383.2997.

*4.9.13. 5-tert-Butyldihydrofuran-2(3H)-one (rac-**22**).*[4,21] Prepared from methyl acrylate (**21**) and trimethylacetaldehyde in 50% yield (Scheme 7). Compound *rac*-**22**: a pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, J=8.4, 7.2 Hz, 1H), 2.59–2.44 (m, 2H), 2.15–2.06 (m, 1H), 2.00–1.89 (m, 1H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 88.2, 33.7, 29.3, 24.8 (×3), 22.9.

4.10. Methylation of *rac*-22

To a solution of diisopropylamine (0.66 mL, 4.74 mmol) in anhydrous THF (4 mL) cooled in a dry ice–acetone bath (–78 °C) under an argon atmosphere was added *n*-BuLi (2 M in cyclohexane, 2.2 mL, 4.40 mmol) dropwise. After stirring at the same temperature for 10 min, the mixture was allowed to warm to room temperature followed by stirring for 1 h to form the LDA solution for the next step.

To a solution of *rac*-**22** (221.5 mg, 1.58 mmol) in anhydrous THF (10 mL) cooled in a dry ice–acetone bath (–78 °C) was added the above freshly prepared LDA solution (4.40 mmol) dropwise followed by stirring at the same temperature for 40 min. To the resultant solution was added MeI (0.30 mL, 4.74 mmol) dropwise. After stirring at –78 °C for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (10 mL×3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 16.7% EtOAc in hexane) to afford *rac*-**20a** (197.5 mg, 80%) as almost a single diastereomer.

4.11. General for epimerization of *trans* isomer to *cis* isomer of 3,5-disubstituted dihydrofuran-2(3*H*)-one

To a solution of *rac*-**20a** (250.0 mg, 1.58 mmol) in anhydrous THF (10 mL) cooled in a dry ice–acetone bath (–78 °C) was slowly added a freshly prepared LDA solution (4.40 mmol) followed by stirring at the same temperature for 1 h. To the resultant mixture at –78 °C was added a solution of 2,6-di-*tert*-butylphenol (1.96 g, 9.48 mmol) in anhydrous THF (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL×3) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 16.7% EtOAc in hexane) to give *rac*-**24** (200.0 mg, 80%, dr>98:2).

*4.11.1. cis-5-tert-Butyl-3-methyldihydrofuran-2(3H)-one (rac-**24**).* Compound *rac*-**24**: a pale-yellow oil; R_f=0.31 (16.7% EtOAc in hexane); IR (film): 2966, 1772, 1479, 1368, 1189, 997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (dd, J=11.2, 6.0 Hz, 1H), 2.73–2.62 (m, 1H), 2.31–2.24 (m, 1H), 1.64–1.55 (m, 1H), 1.27 (d, J=6.8 Hz, 3H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 85.9, 36.2, 33.3, 32.2, 25.1 (×3), 15.1; HRMS (+CI) calcd for $C_9H_{20}NO_2$ 174.1494 ($M+NH_4^+$), found 174.1504.

*4.11.2. cis-5-(2-Phenylethyl)-3-methyldihydro-furan-2(3H)-one (rac-**25**).* Prepared from *rac*-**4b** (*trans*:*cis*=96:4) in 86% yield as a 15:85 mixture of *trans* and *cis* isomers. Compound *rac*-**25**: a pale-yellow oil; R_f=0.32 (16.7% EtOAc in hexane); IR (film): 2934, 1770, 1455, 1186, 1163, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 4.53–4.46 (m, 0.15H), 4.35–4.28 (m, 0.85H), 2.88–2.62 (m, 3.15H), 2.50–2.43 (m, 0.85H), 2.12–1.87 (m, 2H), 1.57–1.48 (m, 1H), 1.27 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ for the major isomer) δ 179.6, 141.0, 128.7 (×2), 128.6 (×2), 126.3, 77.7, 37.4, 37.4, 36.0, 31.8, 15.2; HRMS (+CI) calcd for $C_{13}H_{17}O_2$ 205.1229 ($M+H^+$), found 205.1232.

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Supplementary data

^{1}H and ^{13}C NMR spectra for the compounds **2a**,**c**,**d**, **4b**, **10**, **11**, **12a**,**b**, **13a**–**c**, **20a**–**g**, **24**, **25**, and the related compounds are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.12.009.

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