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Diastereo- and Enantioselective Synthesis of *trans*-2,3-Disubstituted 2,3-Dihydropyran-4-one Derivatives

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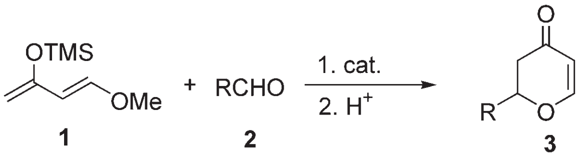
Abstract: *trans*-Diastereoselective hetero-Diels–Alder reactions took place in the presence of $SiCl_4$/activator systems. The reactions of aldehydes with a derivative of Danishefsky's diene afforded the corresponding pyrones with high yields and diastereoselectivity upon activating $SiCl_4$ with suitable neutral Lewis bases. Aldol intermediates deriving from a Mukaiyama-type pathway were isolated in many cases. The employment of a chiral activator allowed us to convert Danishefsky's diene (or its disubstituted derivative) into both aldols and pyrones in good to high enantiomeric excesses.

Keywords: aldol reaction; asymmetric synthesis; diastereoselectivity; enantioselectivity; pyrones; silicon tetrachloride

Introduction

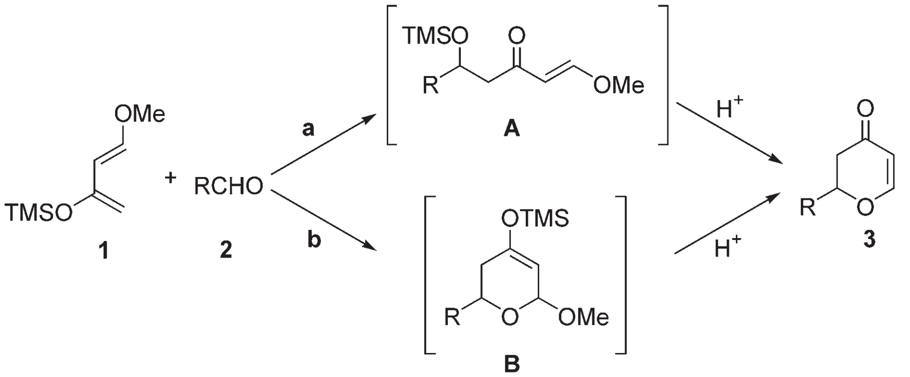
The hetero-Diels–Alder (HDA) reaction represents one of the most powerful tools for the synthesis of racemic or enantiopure pyran derivatives,[1,2] well-known as key intermediates in the preparation of many bio-active compounds.[3] In particular, the HDA reaction of Danishefsky's diene **1** with carbonyl compounds has allowed an easy access to a broad variety of 2,3-dihydro-4*H*-pyran-4-one derivatives of type **3** (Scheme 1).



Scheme 1.

The sequence depicted in Scheme 1 usually requires in the first step the presence of a Lewis acid as catalyst and, accordingly, depending on the used catalytic system, two different mechanistic pathways have been detected (Scheme 2).

A two-step sequence (pathway **a**) involving an initial Mukaiyama aldol reaction, followed by acid-catalyzed cyclization, is typical of B(III),[4] Ti(IV)[5] and Zr(IV)[6] catalysts, while a concerted Diels–Alder reaction has been pointed out in processes promoted by Zn(II),[7] Cr(III),[8] and Eu(III)[9] catalysts (pathway **b**).



Scheme 2.

In the course of an investigation on the reactivity of masked forms of 1,3-dicarbonyl compounds, Danishefsky's diene **1** confirmed its relevant nucleophilic properties, and its vinylogous addition[10] to aldehydes was found to proceed in moderate yields in the presence of a very mild Lewis acid such as SiCl$_4$.[11] In fact, for example, benzaldehyde (**2a**) was converted into the corresponding pyrone derivative **3a** in 56% yield under the conditions depicted in Scheme 3.

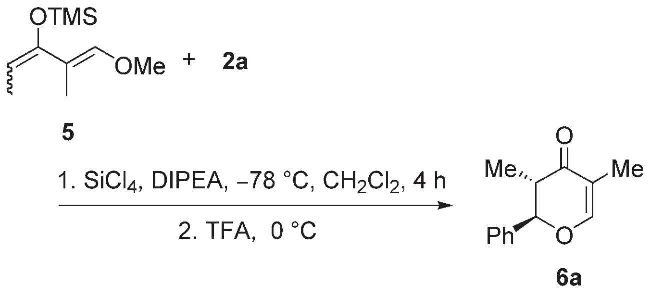
It is noteworthy that a significant enhancement of efficiency (up to 85% yield) in more reduced reaction times was obtained by activating SiCl$_4$ with suitable additives such as sulfoxides, hexamethylphosphoramide (HMPA), dimethylformamide (DMF) and pyridine *N*-oxide (PyN$^+$O$^-$). Rather interestingly from a mechanistic point of view, appropriate quenching, work-up and purification procedures allowed us to obtain several intermediates of type **4** in a rather satisfactory way (57–85% yield) confirming the involvement of a Mukaiyama-type pathway.

In order to expand the synthetic utility of the above protocol, especially as regards the preparative and stereochemical aspects, the reactivity of the Danishefsky's diene derivative **5** was examined. Furthermore, the possibility of achieving an enantioselective version of the vinylogous reaction of dienes **1** and **5** was explored.

Results and Discussion

In the preliminary phase benzaldehyde (**2a**) was chosen as a representative substrate and was submitted to treatment with diene **5** under the typical conditions, as reported in Scheme 4 and Table 1.

A control experiment was performed in the absence of any activator (entry 1) and after the acidic treatment the corresponding pyrone **6a** was obtained in not negligible way (16% yield) in spite of the more enhanced steric hindrance on the reaction site with respect to Danishefsky's diene **1**. More interestingly from a stereochemical point of view, **6a** was isolated almost exclusively as the *trans*-2,3-disubstituted stereoisomer. The activation of SiCl$_4$ by suitable neutral Lewis bases such as methyl *p*-tolyl sulfoxide (entry 2), and DMF (entry 3) proved to be particularly fruitful, while much less satisfactory results were obtained by using HMPA and PyN$^+$O$^-$, respectively, entries 4 and 5. However, in all entries **6a** was attained as the by far predominant *trans*-stereoisomer.



Scheme 4.

Table 1. HDA reaction of diene **5** with benzaldehyde (**2a**).

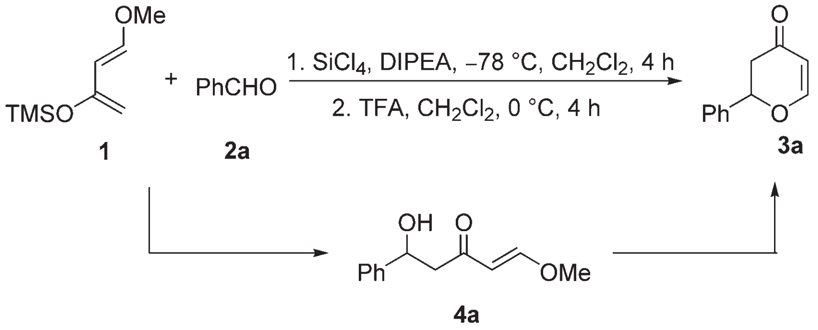
Entry	Activator [0.1 equiv.]	Yield [%][a] **6a**	*trans/cis dr*[b]
1	-	16	>95/5
2	*p*-TolSOMe	95	>95/5
3	DMF	95	>95/5
4	Py-N$^+$O$^-$	64	94/6
5	HMPA	32	95/5

[a] All the yields refer to isolated chromatographically pure compound and are based on the starting **2a**

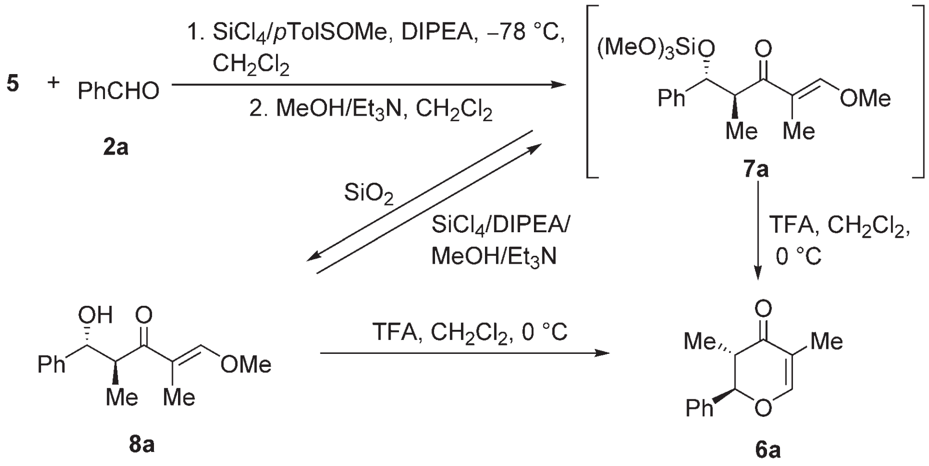
[b] *trans/cis* diastereoisomeric ratios were determined by ^{1}H NMR analysis (400 MHz) on the crude products **6**.

It is notable that in Danishefsky's pioneering work[7] the BF$_3$·Et$_2$O-catalyzed reaction of diene **5** on benzaldehyde afforded the corresponding pyrone **6a** in 90% overall yield as a 76/24 *trans/cis* mixture.

In order to gain further information on the reaction pathway leading to **6a**, benzaldehyde was reacted with diene **5** under the usual conditions (activator methyl *p*-tolyl sulfoxide) and the following acidic treatment was omitted (Scheme 5).



Scheme 3.



Scheme 5.

After quenching with MeOH/Et_3N mixture, the resulting crude product was submitted to ^{1}H NMR analysis (400 MHz), which revealed the almost complete disappearance of the starting materials and the presence of the *O*-protected vinylogous aldol **7a** as only product. In the course of the attempted purification of **7a** by silica gel column chromatography cleavage of the $(MeO)_3Si$- group took place[12] and the *anti*-aldol **8a** was isolated, as a diastereoisomerically pure compound, in satisfactory yield (65%). *anti*-Diastereoselectivity has been already observed in the $SiCl_4$-catalyzed vinylogous aldol condensation of a Chan's diene derivative of type **9** (Figure 1) and was reasonably attributed to a steric interaction between the methyl group and the Lewis acid coordinated to the carbonyl oxygen in an open transition state.[10]

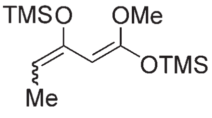


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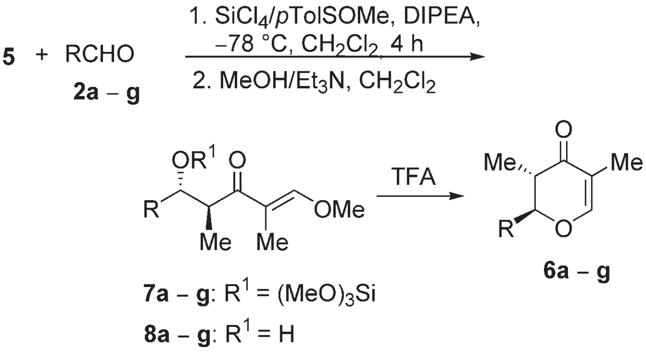
Figure 1.

The conversion **7a**→**8a** proved to be a reversible process since **7a** could be quantitatively obtained by a serial treatment of **8a** with $SiCl_4$/DIPEA and MeOH/Et_3N mixtures in CH_2Cl_2 solution. In every case, both **7a** and **8a** underwent an acid-catalyzed process of cyclization to afford the *trans*-2,3-disubstituted pyrone **6a** in very high yields (>95%).

It is notable that the choice of the activator proved to be critical for an efficient and highly selective production of the aldol **8a**: in fact, in the presence of DMF the aldol reaction proceeded very satisfactorily so that pure *anti*-**8a** could be obtained in 71% yield, as exclusive product. Conversely, the employment of both $SiCl_4$/HMPA and $SiCl_4$/PyN^+O^- catalytic systems led directly to the free aldol **8a** contaminated by a significant amount of the cyclization product **6a**. Particularly, after a fast filtration of the crude reaction mixture on a short pad of silica gel, a 1/1 **6a/8a** mixture was obtained by using PyN^+O^- as activator. However the production of **6a** as exclusive *trans*-diastereoisomer in both the above experiments could be reasonably explained through a Mukaiyama-type pathway involving the not negligible occurrence of a direct cyclization process of **8a** to pyrone **6a** under the conditions used for the vinylogous aldol reaction.

In order to assess the level of general validity of the procedure, several aldehydes were submitted to the usual treatment (Scheme 6) and *rac*-methyl *p*-tolyl sulfoxide was chosen as activator.



Scheme 6.

As reported in Table 2, both the preparative and stereochemical results were found to depend on the aldehyde used: in fact, in entries 1–3 silica gel chromatography on the resulting crude *O*-trimethoxysilyl derivatives **7a–c** afforded the corresponding free aldols **8a–c**, exclusively as *anti*-diastereoisomers, in acceptable yields in spite of a significant tendency to de-

Table 2. $SiCl_4$/*rac*-*p*TolSOMe-catalyzed HDA reaction of diene **5** with different RCHO **2**.

Entry	R	Aldol	Yield [%][a]	Pyrone	Yield [%][b]	*trans/cis dr*[c]
1	Ph	**8a**	65	**6a**	95	>95/5
2	*p*-Cl-C_6H_4	**8b**	54	**6b**	95	>95/5
3	PhCH=CH	**8c**	70	**6c**	80	>95/5
4	*p*-Me-C_6H_4	**8d**	-	**6d**	80	86/14
5	*p*-MeO-C_6H_4	**8e**	-	**6e**	87	89/11
6	*p*-CN-C_6H_4	**8f**	-	**6f**	85	83/17
7	$PhCH_2CH_2$	**8g**	-	**6g**	-	-

[a] All the yields refer to isolated chromatographically pure products **8a–c** (exclusively *anti* diastereoisomers) and are based on the starting RCHO **2.**

[b] The reported values refer to the yields of the overall sequence **2**→**7**→**6** and are based on the starting RCHO **2**.

[c] *trans/cis* diastereoisomeric ratios were determined by ^1H NMR analysis (400 MHz) on the crude products **6**.

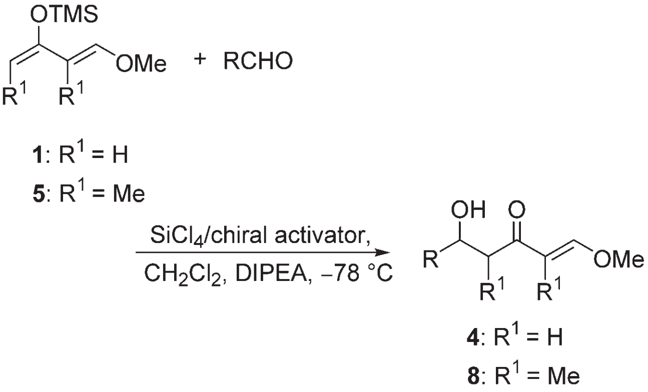
compose in the course of the purification procedure. However, in all the above entries the vinylogous aldol reaction of the diene **5** proved to take place with very satisfactory efficiency since the usual acidic treatment converted the crude intermediates **7a–c** into the *trans*-pyrones **6a–c** in rather good yields (up to 95%) and complete diastereoselectivity.[6,13] Very interestingly, in entries 4–6 the standard procedure ($SiCl_4$/DIPEA/*rac*-*p*TolSOMe) and quenching ($MeOH/Et_3N$) directly led to the pyrones **6d–f**, as by far the predominant *trans*-diastereoisomers in 80–87% yields.

On the ground of the stereochemical outcome, these latter results can be reasonably explained through a very efficient domino process [*anti*-diastereoselective Mukaiyama reaction of diene **5**, desilylation of $(MeO)_3Si$-derivatives **7**, cyclization to *trans*-pyrones **6**] occurring directly in the reaction medium, as previously observed. Furthermore, aliphatic aldehydes proved to be completely unreactive, so that, for example, 3-phenylpropionaldehyde was recovered unchanged after the usual treatment.

The easy and, in some cases, satisfactory accessibility of aldol intermediates of type **4** and **8**, containing several functionalities susceptible of further manipulation, suggested an investigation devoted to the achievement of an enantioselective version of the vinylogous aldol reaction of the dienes **1** and **5**.

Therefore, a set of experiments was performed on different aldehydes by using (*R*)-methyl *p*-tolyl sulfoxide as chiral activator (Scheme 7). Although all the vinylogous aldols of type **4** and **8** could be obtained in acceptable yields (54–64%), unfortunately rather low *ee*s were always observed. For example, the usual treatment afforded respectively (*R*)-**4a** in 64% yield (33% *ee*) and (2*S*,3*R*)-**8a** in 65% yield (17% *ee*).

However, as widely reported in these last years, the activation of $SiCl_4$ by chiral phosphoramides proved to be particularly successful and allowed the realization of an impressive series of related processes for the highly enantioselective C–C bond formation.[14–20]



Scheme 7.

Taking advantage of the easy commercial availability of the chiral ligand (*R,R*)-**10**, the catalytic properties of the $SiCl_4$/(*R,R*)-**10** (Figure 2) system were examined in several vinylogous aldol reactions of dienes **1** and **5**.

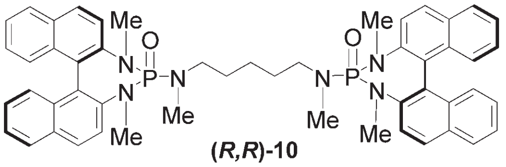


Figure 2.

As reported in Table 3, in the presence of a very reduced chiral ligand (0.01 equiv. with respect to $SiCl_4$) the conversion of Danishefsky's diene **1** into the chiral aldols **4** was found to take place in comparable yields and remarkably improved *ee*s (entries 1–6), in spite of the competing non-asymmetrical background reaction (see Introduction). In the case of the disubstituted diene **5** (entries 7–9) the *anti*-aldols **8** were obtained with complete diastereoselectivity and a

Table 3. Asymmetric aldol reaction of dienes **1** and **5** promoted by $SiCl_4$/(*R,R*)**-10** system.

Entry	R	Reaction time [h]	Product	Yield [%][a]	*ee* [%][b,c]
1	Ph	0.15	**4a**	50	86
2	PhCH=CH	1.5	**4c**	65	53
3	*o*-MeO-C_6H_4	1.0	**4d**	51	87
4	*p*-CF_3-C_6H_4	1.5	**4e**	60	77
5	*p*-Br-C_6H_4	3.0	**4f**	54	78
6	*p*-Me-C_6H_4	2.0	**4g**	60	84
7	Ph	4.0	**8a**	42	81
8	*p*-Cl-C_6H_4	4.0	**8b**	22	78
9	*p*-Me-C_6H_4	4.0	**8d**	52	91

[a] All the yields refer to isolated chromatographically pure aldols **4** or **8** and are based on the starting RCHO **2**. Aldols **8a, b** and **d** were obtained as exclusive *anti*-diastereoisomers.

[b] The *ee* values were determined by HPLC analysis.

[c] The 2(*R*) configuration was assigned to the products **4a**, **c–f** by comparing the sign of the optical rotation of the corresponding pyrones **3a**, **c–f** (obtained through acidic treatment)[4a] with the ones reported in the literature.[21] The (2*R*,3*S*) configuration was assigned to product **8a** by comparing the sign of the optical rotation of the corresponding pyrone **6a** ($[\alpha]_D$: −25.5, *c* 0.7, $CHCl_3$)(obtained by acidic treatment) with the one reported in the literature[22] ($[\alpha]_D$: −27.3, *c* 0.7, $CHCl_3$ for 52% *ee*).The absolute configuration of compounds **8b** and **d** was not assigned.

good to high level of enantioselectivity: the lower efficiency could be again attributed to the lability of intermediates **7** (or the aldols **8**) in the course of the purification by silica gel chromatography. In fact, the usual acidic treatment of the crude product of type **7**, deriving from the vinylogous aldol reaction, afforded the corresponding pyrones **6**, as exclusive *trans*-diastereoisomers, in good yield and almost unchanged *ee*s [**6a** (78% yield, 80% *ee*); **6b** (60% yield, 77% *ee*), **6d** (76% yield, 86% *ee*).

The result obtained in entry 9 pointed out the determining role exerted by the chiral activator in the reaction pathway: in fact, when the same experiment was performed in the presence of $SiCl_4$/(*R*)-methyl *p*-tolyl sulfoxide system, the formation of the pyrone **6d** (84/16 *trans/cis* ratio, 23% *ee* of the predominant diastereoisomer) was found to occur directly under the conditions used for the vinylogous aldol reaction.

Conclusions

In conclusion, *trans*-2,3-disubstituted pyrone derivatives proved to be easily accessible with a high level of diastereoselectivity by a new procedure based on the vinylogous aldol reaction of a Danishefsky's diene derivative, promoted by $SiCl_4$/neutral Lewis base systems. The corresponding *anti*-aldol intermediates could be isolated in a satisfactory way in several cases, confirming the involvement of a Mukaiyama-type pathway. The employment of a chiral $SiCl_4$/bisphosphoramide catalyst proved to be successful, usually allowing the production of the intermediate vinylogous aldols of type **4** in a satisfactory way and good to high enantiomeric excesses. In the case of the dimethyl-substituted Danishefsky's diene **5** comparable levels of enantioselectivity and complete *anti*-diastereoselectivity could be observed for the corresponding aldols **8** whose acid-catalyzed conversion into the chiral *trans*-pyrones **6** took place very efficiently and no significant modification of optical purity.

Experimental Section

General Remarks

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry nitrogen. All the solvents for the reactions were of reagent grade and were dried and distilled immediately before use (dichloromethane from calcium hydride). Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The chiral phosphoramide ***R,R*-10**, commercially available from Obiter Research, LLC, and the other reagents (Aldrich and Fluka) were used without further purification. The NMR spectra were recorded on a Bruker DRX 400 (400 MHz, ^1H; 100 MHz, ^{13}C). Spectra were referenced to residual chloroform (7.26 ppm, ^1H, 77.23 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. HPLC analyses were performed with Waters Associates equipment (Waters 2487 Dual λ absorbance Detector) and using a CHIRALPAK AD or a CHIRALCEL OD column with hexane/isopropyl alcohol mixtures and flow rates as indicated. The HPLC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured with a JASCO DIP-1000 polarimeter. Mass spectrometry analysis was carried out using an electrospray spectrometer Waters 4 micro quadrupole.

General Procedure for the Enantioselective Vinylogous Addition of Danishefsky's Diene 1 (or Diene 5)

In a flame-dried, 2-necked, round-bottom flask, diisopropylethylamine (1.34 mmol), $SiCl_4$ (1.34 mmol) and the aldehyde (1.34 mmol) were successively added at −78 °C under argon to a solution of chiral activator (0.013 mmol) in dry CH_2Cl_2 (6 mL). Then, Danishefsky's diene **1** (or **5**) (1.48 mmol) was slowly added over a period of 5 min. The reaction was stirred at −78 °C for the time reported in Scheme 6. At the end of the reaction, a mixture of $MeOH/Et_3N = 0.2/0.3$ mL was added at −78 °C and the resulting mixture was allowed to stir at 0 °C until the formation of a precipitate. Then 5 mL of petroleum ether/AcOEt (8/2) solution were added and the mixture was filtered and washed with petroleum ether/AcOEt (8/2) (5 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel with a petroleum ether-AcOEt mixture (from 95/5 to 8/2) to afford the pure aldols **4** (or **8**).

The same procedure was used for non-asymmetric vinylogous reactions by omitting the employment of the chiral activator.

General Procedure for the Conversion of Aldols 4 (or 8) to Pyrones 3 (or 6)

The crude product obtained from the vinylogous addition (or the purified aldol) was dissolved in 10 mL of CH_2Cl_2 at 0 °C and a solution of trifluoroacetic acid (0.15 mL) in CH_2Cl_2 (1 mL) was added and the mixture was allowed to stir for 3 h at this temperature. Then saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (25 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography (petroleum ether-AcOEt mixtures, from 95/5 to 8/2) to afford the desired product.

The spectroscopic (IR, ^1H NMR and ^{13}C NMR) data of aldols **4a–d** matched the ones reported in the literature.[10]

Aldol (2*R*)-4a: $[\alpha]_D^{25}$: +57° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4a** was determined to be 86% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 46.2$ min for major enantiomer; $t_R = 51.0$ min for minor enantiomer. Absolute configuration was assigned as ***R*** by comparison of the sign of the optical rotation of the corresponding γ-pyrone, obtained by acidic treatment according to ref.[4a] with the one reported in the literature.[20]

Aldol (2*R*)-4b: $[\alpha]_D^{25}$: +1° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4b** was determined to be 21% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 56.9$ min for major enantiomer; $t_R = 60.5$ min for minor enantiomer. Absolute configuration was assigned as ***R*** by comparison of the sign of the optical rotation of the corresponding γ-pyrone, obtained by acidic treatment according to ref.[4a] with the one reported in the literature.[20]

Aldol (2*R*)-4c: $[\alpha]_D^{25}$: +10° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4c** was determined to be 53% by HPLC with a Diacel Chiralpak AD column (9/1 hexane/*i*-PrOH, 0.5 mL min^{-1}): $t_R = 67.3$ min for major enantiomer; $t_R = 73.6$ min for minor enantiomer. Absolute configuration was assigned as ***R*** by comparison of the sign of the optical rotation of the corresponding γ-pyrone, obtained by acidic treatment according to ref.[4] with the one reported in the literature.[20]

Aldol 4d: $[\alpha]_D^{25}$: +77° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4d** was determined to be 87% by HPLC with a Diacel Chiralpak AD column (9/1 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 59.0$ min for major enantiomer; $t_R = 72.1$ min for minor enantiomer. The absolute configuration of **4d** was not assigned.

Aldol 4e: IR (KBr): ν = 3376, 1718, 1676, 1617, 1588, 833 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.83$ (m, 2H), 3.71 (s, 3H), 5.15 (m, 1H), 5.57 (d, $J = 12.8$ Hz, 1H), 7.48 (d, $J = 8.1$ Hz, 2H), 7.59 (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 48.8$, 57.7, 69.6, 105.6, 120.1, 125.5 (2C), 127.6 (2C), 129.9, 147.0, 163.9, 198.9. $[\alpha]_D^{25}$: +44° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4e** was determined to be 77% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 42.4$ min for major enantiomer; $t_R = 37.8$ min for minor enantiomer. The absolute configuration of **4e** was not assigned.

Aldol 4f: IR (KBr): ν = 3421, 1718, 1676, 1619, 1590, 821, 701 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.85$ (m, 2H), 3.70 (s, 3H), 5.15 (m, 1H), 5.57 (d, $J = 12.6$ Hz, 1H), 7.26–7.36 (m, 4H), 7.60 (d, $J = 12.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 49.0$, 57.7, 70.2, 105.9, 126.5 (2C), 128.5, 130.0 (2C), 143.0, 163.8, 199.4; anal. calcd. for $C_{13}H_{13}BrO_3$: C 50.55, H 4.60; found: C 50.60, H 4.55. $[\alpha]_D^{25}$: +34° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4f** was determined to be 76% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 64.7$ min for major enantiomer; $t_R = 61.6$ min for minor enantiomer. The absolute configuration of **4f** was not assigned.

Aldol 4g: IR (KBr): ν = 3421, 1675, 1617, 1590, 817 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.34$ (s,3H), 2.85 (m, 2H), 3.70 (s, 3H), 5.14 (m, 1H), 5.58 (d, $J = 12.7$ Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.62 (d, $J = 12.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 49.0, 57.6, 70.1, 105.9, 125.6, 129.1, 137.2, 140.1, 163.7, 199.4; anal. calcd. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.95, H 7.30. $[\alpha]_D^{25}$: +93° (*c* 1.0, $CHCl_3$). Enantiomeric excess of **4g** was determined to be 84% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 61.5$ min for major enantiomer; $t_R = 66.8$ min for minor enantiomer The absolute configuration of **4g** was not assigned.

Aldol (2*R*,3*S*)-8a: *anti* isomer: IR (KBr): ν = 3418, 1720, 1635, 1599, 1098, 871, 705 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.06$ (d, $J = 7.1$ Hz, 3H), 1.68 (s, 3H), 3.24 (m, 1H), 3.83 (s, 3H), 4.85 (d, $J = 6.9$ Hz, 1H), 7.16 (s, 1H), 7.3–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 8.1$, 16.5, 29.6, 46.7, 61.4, 117.2, 126.3, 127.5, 128.2, 142.7, 160.7, 204.1; MS-ES: $m/z = 257$ $[M+Na]^+$; $[\alpha]_D^{22}$: +83.0 (*c* 0.5, $CHCl_3$). Enantiomeric excess of **8a** was determined to be 81% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 29.3$ min for minor enantiomer; $t_R = 36.1$ min for major enantiomer. The absolute configuration of **8a** was assigned as reported in Table 3, footnote [c].

Aldol 8b: *anti* isomer: IR (KBr): $\nu = 3420$, 1718, 1670, 1633, 1595, 860, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.06$ (d, $J = 7.1$ Hz, 3H), 1.66 (s, 3H), 3.18 (m, 1H), 3.84 (s, 3H), 4.81 (bd, 1H), 7.15 (s, 1H), 7.26 (m, 4H); ^{13}C NMR ($CDCl_3$): $\delta =$ 8.1, 16.5, 29.5, 46.5, 61.5, 117.1, 127.6, 128.3, 133.1, 141.3, 160.8, 203.9; MS-ES: $m/z = 291$ $[M+Na]^+$. $[\alpha]_D^{24}$: +7.4 (*c* 0.4, $CHCl_3$). Enantiomeric excess of **8b** was determined to be 78% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 23.9$ min for minor enantiomer; $t_R = 30.6$ min for major enantiomer. The absolute configuration of **8b** was not assigned.

Aldol 8d: *anti* isomer: IR (KBr): $\nu = 3421$, 1718, 1671, 1635, 1595, 862, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 1.03$ (d, $J = 7.0$ Hz, 3H), 1.69 (s, 3H), 2.33 (s,3H), 3.22 (m, 1H), 3.84 (s, 3H), 4.82 (d, $J = 7.1$ Hz, 1H), 7.14 (d, $J = 7.9$ Hz, 2H), 7.18 (s, 1H), 7.22 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 8.2$, 16.5, 21.0, 29.6, 46.7, 61.4, 117.2, 126.2, 128.9, 137.1, 139.6, 160.6, 204.1; MS-ES: $m/z = 271$ $[M+Na]^+$; $[\alpha]_D^{24}$: +93.0 (*c* 0.25, $CHCl_3$). Enantiomeric excess of **8d** was determined to be 91% by HPLC with a Diacel Chiralpak AD column (95/5 hexane/*i*-PrOH, 0.6 mL min^{-1}): $t_R = 25.0$ min for minor enantiomer; $t_R = 31.4$ min for major enantiomer. The absolute configuration of **8d** was not assigned.

The spectroscopic (IR, ^{1}H NMR and ^{13}C NMR) and analytical data of *trans*-pyrones **6a–d** matched the ones reported in the literature.[6,13,21]

Pyrone 6e: *trans* isomer: ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (d, $J = 7.0$ Hz, 3H), 1.72 (s, 3H), 2.78 (dq, $J = 13.5$; 7.0 Hz, 1H), 3.82 (s, 3H), 4.87 (d, $J = 13.5$ Hz, 1H), 6.92 (d, $J = 6.5$ Hz, 2H), 7.29 (s, 1H), 7.30 (d, $J = 6.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 11.7, 45.6, 56.2, 87.5, 114.0, 115.0, 129.7, 130.7, 159.8, 161.0, 196.2; MS-ES: $m/z = 255$ $[M+Na]^+$.

Pyrone 6f: ^{1}H NMR ($CDCl_3$): *trans* isomer: $\delta = 0.93$ (d, $J = 6.9$ Hz, 3H), 1.72 (s, 3H), 2.72 (dq, $J = 13.2$; 6.9 Hz, 1H), 4.96 (d, $J = 13.2$ Hz, 1H), 7.30 (s, 1H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.61 (d, $J = 8.1$ Hz, 2H); *cis* isomer: $\delta = 0.86$ (d, $J = 7.2$ Hz, 3H), 1.75 (s, 3H), 2.61 (dq, $J = 7.2$; 3.1 Hz, 1H), 5.50 (d, $J = 3.1$ Hz, 1H), 7.38 (s, 1H), 7.46 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$); *trans* isomer: $\delta = 11.2$, 11.6, 45.7, 86.8, 113.9, 114.6, 119.2, 129.0, 133.5 143.6, 159.1, 194.8; *cis* isomer: $\delta = 10.2$, 10.5, 44.6, 85.7, 112.7, 113.5, 118.2, 127.4, 132.3 142.5, 158.1, 193.7; MS-ES: $m/z = 250$ $[M+Na]^+$.

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