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Highly Substituted Tetrahydropyrones from Hetero-Diels–Alder Reactions of 2-Alkenals with Stereochemical Induction from Chiral Dienes

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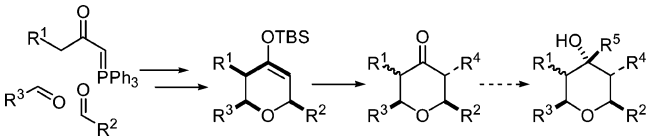

A new method for the stereoselective synthesis of libraries of 2,3,5-trisubstituted tetrahydro-γ-pyrones and the corresponding tetrahydropyran-4-ols is reported. Dienes with a chiral moiety at position 5 were synthesized starting from (triphenylphosphoranylidene)acetone. In hetero-Diels–Alder (HDA) reactions, especially with α,β-unsaturated aldehydes, they induce diastereomeric ratios from 4:1 to 14:1. Through selective epimerization and reduction, further building blocks are available. These constitute ideal starting points for their use in the total synthesis of complex polyketide macrocycles, especially with the vinyl group available for metathetic coupling.

Substituted di- and tetrahydropyran rings are frequently occurring structural motifs in biologically active natural products, including laulimalide (**1**),[1–5] the bryostatins (**2a**,**b**),[6,7] the phorboxazoles (**3**), and ratjadone (**4**) (Scheme 1).[8,9] Commonly, in the 4-position an oxygen substituent is encountered, as would be expected from polyketide metabolism, which is the origin of almost all pyran-containing natural products. The remarkable biological activity of these compounds makes them attractive targets for synthetic chemists. There are, however, few generally applicable synthetic routes to such highly substituted tetrahydropyran systems.

Recently, the Prins cyclization and related reactions have received significant attention as a means for the (asymmetric) synthesis of tetrahydropyran derivatives.[10–14] An important advantage of this methodology is the possibility to construct tetrahydropyrans in one step from readily available starting materials (e.g., homoallylic alcohols and simple aldehydes), and in some cases yield and diastereoselectivity are excellent.[13] The major drawback is the formation of side products, probably arising from an oxonia-Cope-type rearrangement, especially when substituents at the 2- or 6-position stabilize the cationic intermediate.[15,16]

Another possibility of constructing a new carbon–carbon bond and the ring ether in a single step is provided by the hetero-Diels–Alder (HDA) reaction.[17,18] In the 1980s, Danishefsky et al. demonstrated the synthetic potential of this reaction.[19] Up to three new stereocenters can be formed, and several chiral HDA catalysts (including chiral aluminum[20] and boron[21] complexes) have been developed to control the stereochemical outcome. Most of these, however, require doubly activated dienes such as Danishefsky's diene [1-methoxy-3-(trimethylsilyloxy)butadiene] as substrate, which limits their applicability substantially. Only Jacobsen's recently developed Cr(III) catalyst accepts monoactivated dienes as substrates.[22] Paterson and Lockhurst recently demonstrated that this catalyst may also be applied in more complex systems, using a catalytic asymmetric HDA reaction for the construction of a phorboxazole A fragment.[23] However, applicability still seems to be limited, depending on the nature of the aldehyde and steric bulk of either of the substrates.

In these catalytic asymmetric methods, especially α,β-unsaturated aldehydes lack reactivity, and typically doubly activated dienes are required as reaction partners. Their incorporation is highly desirable, since the resulting exocyclic vinyl group provides the THP-building block with a handle for metathetic connection or macrocyclization procedures. Unfortunately, to the best of our knowledge, no diastereo- or enantioselective HDA reaction of

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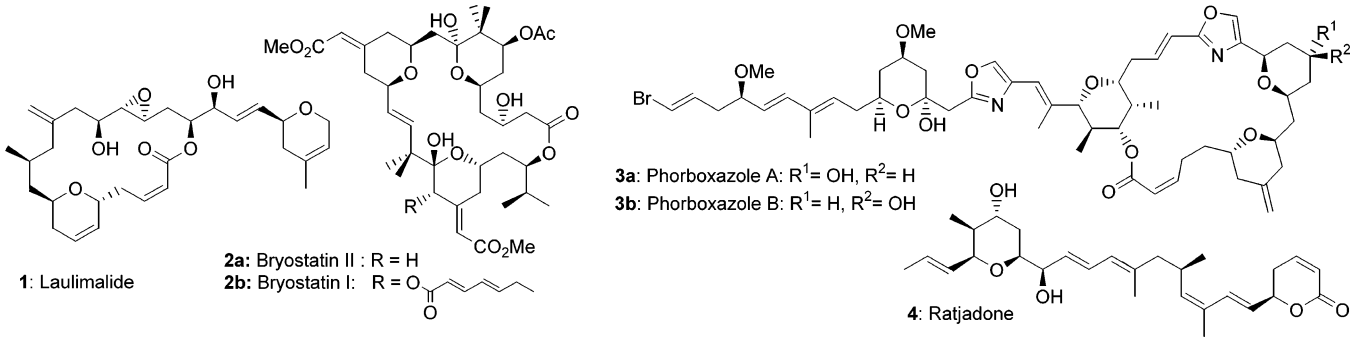
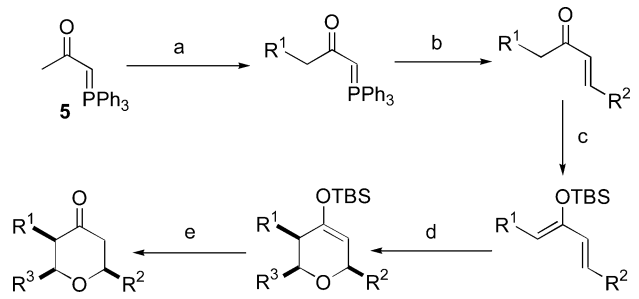
SCHEME 1



SCHEME 2. Versatile Synthesis of 2,3,5-Trisubstituted Tetrahydro-4-pyrones[a]



[a] Key: (a) *n*-BuLi, R^1I, THF, −78 °C to rt; (b) R^2CHO, CH_2Cl_2; (c) TBSOTf, Et_3N, Et_2O, 0 °C; (d) R^3CHO, $BF_3{\cdot}Et_2O$, Et_2O, −30 °C; AcOH, TBAF, THF.

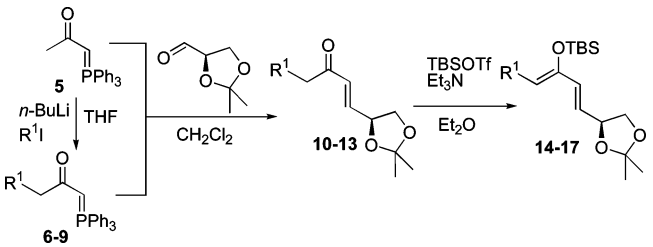
α,β-unsaturated aldehydes with monoactivated dienes has been described so far.

Another means of controlling the stereochemical outcome of the HDA reaction is the use of enantiomerically pure starting materials. Several examples of asymmetric HDA reactions with enantiomerically pure chiral aldehydes have been described.[24,25] Martin et al. have demonstrated a synergistic effect between a chiral aldehyde and a chiral diene.[26] Also, Hu et al. described an asymmetric HDA reaction using a chiral diene and a chiral Co(II) salen catalyst.[27] However, to the best of our knowledge, the use of a chiral diene as sole means of controlling the stereochemical outcome of the HDA reaction has not been described to date.

We now report a stereoselective route to all-cis 2,3,6-trisubstituted tetrahydro-γ-pyrones and related enol ethers and alcohols using an HDA reaction between enantiomerically pure chiral dienes and α,β-unsaturated aldehydes. The general strategy is outlined in Scheme 2.

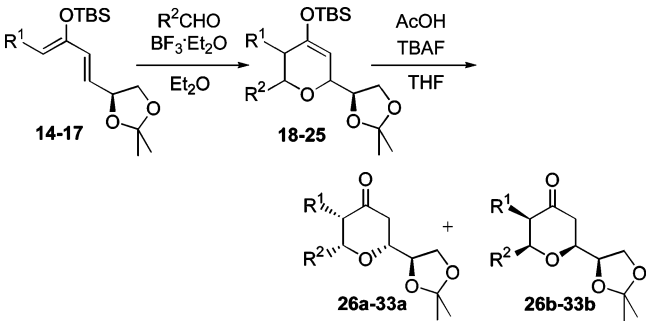
β-Keto ylides **6**−**9** were obtained by alkylation of commercially available ylide **5** with the appropriate alkyl iodides after deprotonation with *n*-BuLi (Table 1).[28] Enones **10**−**13** were obtained by Wittig reaction of ylides **5**−**8** with aldehydes, especially with (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (available in two steps from inexpensive mannitol[29,30]) as summarized in Table 2. In all cases, only the *E*-enone was isolated; the *Z*-product was either absent or present as a very minor impurity that was easily removed by flash chromatography. This is in contrast to a literature report where **10** was formed

TABLE 1. Preparation of Dienes



entry	ylide	R^1 =	ylide yield (%)	enone	enone yield (%)	diene	diene yield (%)
1	**5**	H		**10**	80	**14**	95
2	**6**	Me	94	**11**	42	**15**	88
3	**7**	Et	88	**12**	43	**16**	93
4	**8**	*i*Pr	100	**13**	54	**17**	93
5	**9**	*i*Bu	95				

TABLE 2. Hetero-Diels−Alder (HDA) Reaction of 2-Alkenals



entry	diene	R^1 =	R^2 =	HDA product	THP-4-one	yield (% over two steps)
6	**14**	H	$CH_3CH{=}CH$	**18**	**26**	78
7	**14**	H	$PhCH{=}CH$	**19**	**27**	85
8	**15**	Me	$CH_3CH{=}CH$	**20**	**28**	84
9	**15**	Me	$PhCH{=}CH$	**21**	**29**	85
10	**16**	Et	$CH_3CH{=}CH$	**22**	**30**	84
11	**16**	Et	$PhCH{=}CH$	**23**	**31**	72
12	**17**	*i*Pr	$CH_3CH{=}CH$	**24**	**32**	77
13	**17**	*i*Pr	$PhCH{=}CH$	**25**	**33**	69

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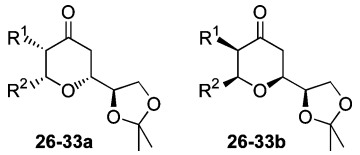
TABLE 3. Diastereoselectivity of 2-Alkenal−HDA Reactions



			HDA product	
entry	R^1 =	R^2 =	no.	ratio **a/b**
14	H	$CH_3CH{=}CH$	**26**	2:1
15	H	PhCH=CH	**27**	1.6:1
16	Me	$CH_3CH{=}CH$	**28**	4:1
17	Me	PhCH=CH	**29**	10:1
18	Et	$CH_3CH{=}CH$	**30**	7:1
19	Et	PhCH=CH	**31**	8:1
20	*i*Pr	$CH_3CH{=}CH$	**32**	7:1
21	*i*Pr	PhCH=CH	**33**	4:1

in a 3:1 *E*/*Z* ratio.[27] The sometimes mediocre yields are caused by difficulties in the purification of the β-keto ylides, a problem that should not prevail if large scales are required, or isolation and purification are omitted. Enones **10**−**13** were then smoothly converted to the corresponding TBS enol ethers **14**−**17**. Racemization was not observed, but partial racemization cannot be excluded if, e.g., triethylamine is applied in excess for extended periods.

Hu et al. reported that treatment of **14** with $BF_3{\cdot}Et_2O$ resulted in decomposition.[27] Although we found this to be the case at room temperature, $BF_3{\cdot}Et_2O$-mediated decomposition of silyloxydienes **14**−**17** was not observed at temperatures below −20 °C. Thus, dienes **14**−**17** were subjected to $BF_3{\cdot}Et_2O$-mediated HDA reaction with crotonaldehyde or cinnamaldehyde at temperatures between −20 and −35 °C. The resulting dihydropyrans **18**−**25** were desilylated with TBAF, which was acidified with 2.5 equiv of AcOH to prevent partial epimerization at C3 to give tetrahyropyran-4-ones **26**−**33** (Table 2).

Yields (Table 2) and diasteromeric ratios (Table 3) of the HDA products range from good to excellent. The isolated tetrahydropyran-4-ones were typically mixtures of the two isomers that have all-cis configuration of the ring substituents. This was confirmed by NOE spectroscopy for **33a** (Figure 1, Supporting Information) and based on analogy of ^{1}H NMR coupling constants for the other tetrahydropyran-4-ones **26**−**32** and **33b**. Diastereomeric ratios for compounds **26**−**33** were determined from the amounts of the pure, isolated diastereomers and are summarized in Table 3. Traces of a third diastereomer could be observed for **26**, **27**, and **33**. Only the latter could be separated from the β-isomers and probably is the 2,6-trans-isomer with a downfield-shifted H-6.

It should be noted that compounds such as **26**−**33** (i.e., with a 2- or 6-alkenyl substituent) are not available through the alternative HDA reaction, disconnecting at the other side of the oxygen. In this case, the required diene would be a conjugated triene, which does not react properly in HDA reactions. Thus, the current method provides access to a class of compounds that was previously inaccessible by related methods.

HDA reaction of diene **14** with ethyl glyoxylate under various conditions, including Co(II) salen catalysis, has been reported to afford not only both cis diastereomers, but both trans isomers as well.[27] These results suggest that the products arise from a tandem Mukaiyama−Michael-type addition, rather than a (pseudo-)concerted [4 + 2] cycloaddition. HDA reactions with α,β-unsaturated aldehydes (typically less reactive than ethyl glyoxylate) reported here generally afford only the all-cis isomers, and thus most likely proceed through a more selective (pseudo-)concerted [4 + 2] cycloaddition mechanism.

The absolute stereochemistry of the tetrahydropyranones was assigned on the basis of the conversion of **28a** (major isomer) to **35a** (Scheme 3). K-Selectride reduction of **28a** afforded a 1:4 mixture of axial alcohol **34a** and equatorial alcohol **34b**. Axial/equatorial assignments were made on the basis of ^{1}H NMR coupling constants. Also, the presence of an axial C4 alcohol causes a characteristic downfield shift of H^2 and H^6. Subsequent acetonide cleavage of **34a** gave triol **35a**, which was shown by ^{1}H NMR to be nonidentical to known **35b**.[9]

Further evidence for the exclusive formation of the all-cis products was supplied by HDA reaction of achiral dienes **38** and **39** (i.e., with an isopropyl group instead of the dimethyldioxolane substituent) with crotonaldehyde or cinnamaldehyde (Scheme 4). Here, only one pair of (enantiomeric) diastereomers of the desilylated HDA products **40**−**42** was formed. The all-cis configuration was confirmed by NOE spectroscopy for **41** and based on analogy of ^{1}H NMR coupling constants for the other tetrahydropyran-4-ones **40** and **42**.

Interestingly, reaction of diene **44**, which has an aromatic ring conjugated to the diene system, with crotonaldehyde and cinnamaldehyde gave the classical Diels−Alder adducts **45** and **46** as the sole isolated products, rather than the expected HDA products (Scheme 5).

A possible rationalization for this observation is a decrease in the HOMO energy of the diene through conjugation to the aromatic ring.

An expansion of the applicability of the current methodology would be the selective base-catalyzed epimerization at C3. Especially in the case of a bulky substituent, the equatorial position should be favored over the axial one. Indeed, when **33a** was treated with base, it was slowly converted to **33c** (Scheme 6). The product was shown to be different from **33a** and **33b** (and the abovementioned third unidentified isomer) by ^{1}H and ^{13}C NMR, showing coupling constants typical for a trans relationship of the C2 and C3 substituents.

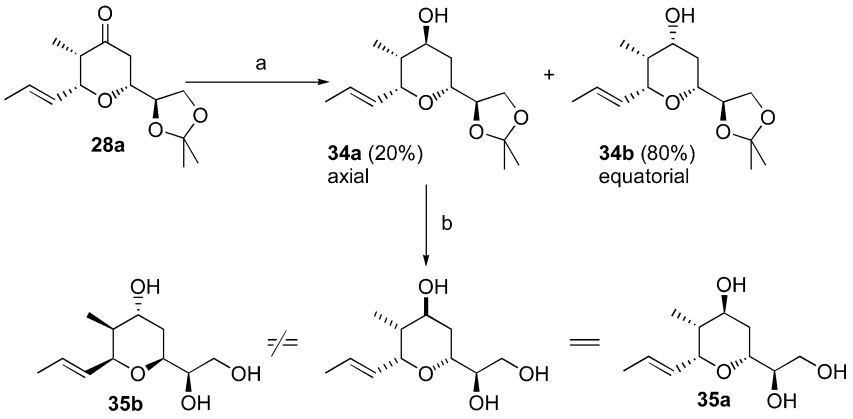
Even though the recovery rate needs to be improved, the isomerization provides easy access to related tetrahydropyran-4-ones with different relative configuration.

Another method to increase diversity of this strategy is nucleophilic addition to the ketone function. As an example, **27a** was reacted with MeMgBr to afford a single diastereomer of tertiary alcohol **47** (Scheme 7). The excellent diastereoselectivity is presumably caused by the adjacent axial methyl group, which makes equatorial attack unfavorable.

Also in this case, the yields are not optimized. However, this reaction demonstrates that the described tetrahydro-γ-pyrones can be easily and selectively modified by nucleophilic addition.

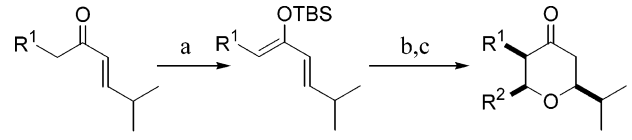
Finally, quenching the HDA-products with other electrophiles than protons provides a further possible expansion. The Mukaiyama-type aldol reaction of the intermediate TBS enol ether may be used to modify position

SCHEME 3. Assignment of the Induced Stereochemistry[a]



[a] Key: (a) K-Selectride, THF, −78 °C (100%, eq/ax = 80:20); (b) PPTS, acetone/H_2O 1:1, 58%.

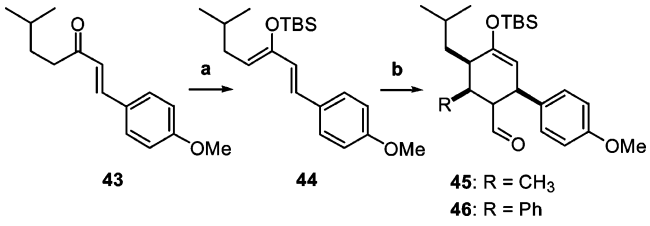
SCHEME 4[a]



36: R^1 = Et
37: R^1 = *i*Bu
38: R^1 = Et
39: R^1 = *i*Bu
40: R^1 = Et, R^2 = $CH_3CH{=}CH$
41: R^1 = Et, R^2 = PhCH=CH
42: R^1 = *i*Bu, R^2 = PhCH=CH

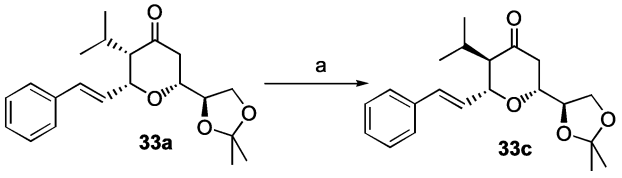
[a] Key: (a) TBSOTf, Et_3N, Et_2O; (b) R^2CHO, $BF_3{\cdot}Et_2O$, Et_2O; (c) AcOH, TBAF, THF.

SCHEME 5[a]



[a] Key: (a) TBSOTf, Et_3N, Et_2O; (b) RCH=CHCHO, $BF_3{\cdot}Et_2O$, Et_2O, −30 °C.

SCHEME 6. Epimerization at C-3[a]

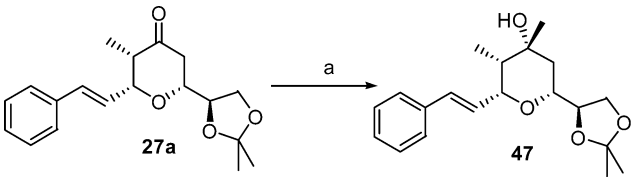


[a] Key: (a) KOtBu, MeOH, 2 d (53%).

5. More details will be reported in a forthcoming publication.

In conclusion, we described the synthesis of a diene controlled asymmetric hetero-Diels−Alder reaction of α,β-unsaturated aldehydes with full chemo- and regioselectivity and good to excellent diastereoselectivity. The presented method allows the stepwise introduction of three substituents and a fourth one based on the enol ether (position 5) or the 4-oxo group. It is therefore of use for the construction of combinatorial libraries of 2,3,6-substituted tetrahydro-γ-pyrones, 2,3,5,6-substituted tetrahydro-γ-pyrones, and the corresponding tetrahydropyran-4-ol derivatives. The presented compounds can serve as building blocks for polyketide type compounds because they allow a differential coupling to the substituents of the crucial 2-position and 6-position. Thus, the 2-alkenyl group is suitable for further coupling via metathesis reaction, whereas the 6-position principally can be provided with any type of connection handle, e.g., an alcohol (→ aldehyde or halide).

SCHEME 7. Functionalization at C-4[a]



[a] Key: (a) MeMgBr, THF (52%).

Experimental Section

General Procedure for HDA Reactions with Alkenals. To a solution of a diene in Et_2O the alkenal (1.5 equiv) was added at −30 °C followed by $BF_3{\cdot}Et_2O$ (1.5 equiv). The mixture was stirred at −20 to −30 °C for 1.5−4 h, quenched by addition of Et_3N (3 equiv), diluted with water (50 mL), and extracted with tBuOMe (3 × 35 mL). The combined organic fractions were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude HDA products which were analyzed by ^1H NMR for identity and diastereomeric ratio of the products, and used in the next step without further purification.

For desilylation, to the TBS enol ethers in THF were added acetic acid (2.5 equiv) and $TBAF{\cdot}3H_2O$ (1.5 equiv) at 0 °C. The mixture was stirred at room temperature until the starting material had been consumed (TLC). The mixture was diluted with satd aq $NaHCO_3$ solution (50 mL) and extracted with tBuOMe (3 × 35 mL). The combined organic fractions were dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by flash chromatography on silica.

Acknowledgment. We thank Dr. A. Porzel for NOESY measurements and assistance in confirming relative configurations. E.R. is thankful for financial support from an EU grant (Combiocat) and HWP support from the state of Saxony-Anhalt.

Supporting Information Available: General experimental procedures and detailed experimental and characterization data (^1H and ^{13}C NMR and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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