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Enantiomerically pure P-chiral dicyclohexylammonium 2-(phosphinyl)acrylates as new Michael acceptors. Enantioselective synthesis of α-methylene-δ-valerolactones

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Abstract—A convenient method for the preparation of enantiomerically pure P-chiral dicyclohexylammonium 2-(phosphinyl)acrylates **6** and **7** is presented. The synthesis of α-methylene-δ-valerolactone **5a** with enantiomeric excesses of 85% and 80% has been developed. The key step of the synthesis involves an asymmetric Michael addition of imine **10** to acrylates **6** and **7**, respectively.

1. Introduction

In recent years, stereodifferentiating reactions occurring with a transfer of chirality from phosphorus to carbon have emerged as a valuable approach to the synthesis of various nonracemic organic compounds. A number of reagents with P-chiral phosphonate, phosphonoamidate and phosphonoamide auxiliaries effecting such a transfer have been reported.[1] In contrast, much less attention has been paid to P-chiral phosphinates. Early studies from our laboratory focused on the use of methyl *O*-methylphenylphosphinyl acetate in Horner–Wadsworth–Emmons type synthesis of enantiomerically enriched allenes and cycloalkylideneacetates.[2] However, the scope of this methodology, owing to poor stereoselectivity, appeared rather limited. Since then, no attempts with regards to the application of phosphinates as P-chiral reagents have been made.

The substrate-controlled diastereoselective Michael addition of enamines derived from 2-substituted cycloalkanones and enantiomerically pure amines to electron-deficient alkenes remains a strategic choice for highly enantioselective construction of a quaternary stereogenic center adjacent to a carbonyl group.[3] Among the chiral primary amines used for this purpose, 1-phenylethylamine has gained a prominent position.

We have recently reported that enamines **2** derived from 2-substituted cycloalkanones **1** and this amine react with dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **3** to provide highly enantioenriched 2-diethoxyphosphoryl-5-oxoalkanoic acids **4** (Scheme 1).[4] It has been proven that acids **4** form as mixtures of epimers with the same absolute configuration at the quaternary stereogenic center. In order to demonstrate the utility of our methodology, we employed this addition as a key reaction in the enantioselective synthesis of α-methylene-δ-valerolactones **5**. We have shown that the sequence involving diastereoselective reduction of the carbonyl group of acids **4**, followed by lactonization, and finally Horner–Wadsworth–Emmons olefination of the resulting α-phosphono-δ-valerolactones provides the corresponding α-methylene-δ-valerolactones **5** with 96–97% enantiomeric excess.

Surprisingly, the literature contains only a few examples of a reagent-controlled asymmetric Michael reaction that takes advantage of acceptors containing chiral directing groups for the construction of a quaternary stereogenic center adjacent to a carbonyl group.[5] We envisioned that chiral bicyclic lactones **5** could become available through a Michael addition of enamines, derived from achiral amines, to dicyclohexylammonium 2-(phosphoryl)acrylate bearing a stereogenic phosphorus center. The present work

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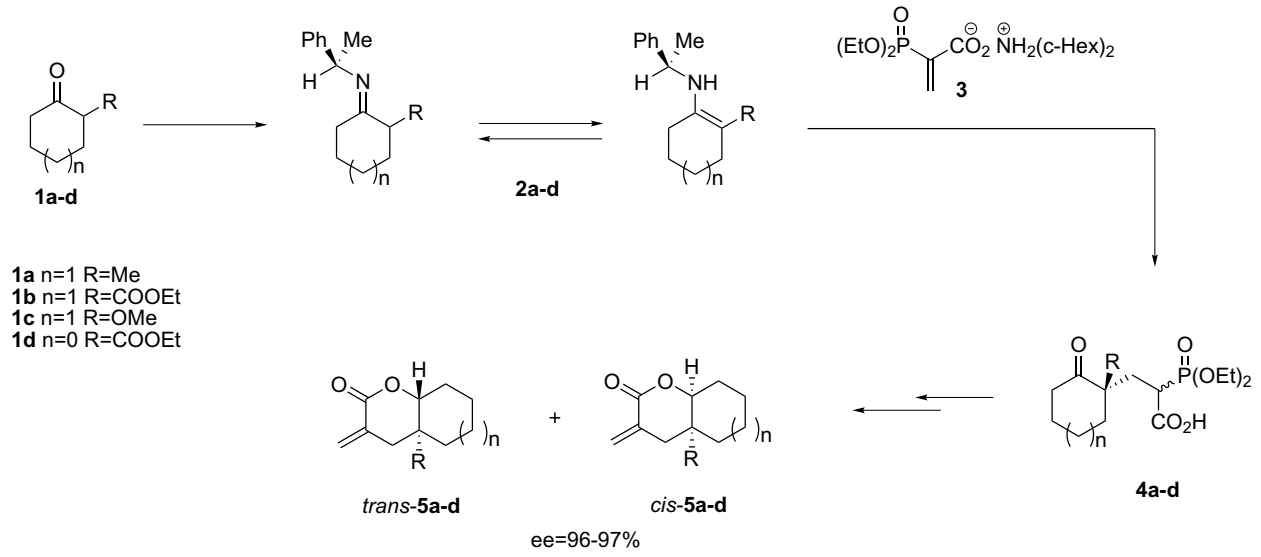
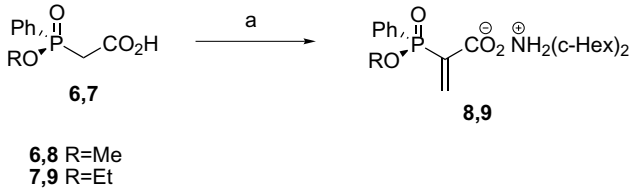


Scheme 1.



Scheme 2. Reagents and conditions: (a) $(C_6H_{11})NH$ (1 equiv), $(HCHO)_n$ (2 equiv), Et_3N (1 equiv), benzene, reflux, 45 min, 70%.

has been undertaken to initiate the exploration of such a methodology.

P-Chiral, enantiomerically pure analogues of acrylate **3** have not yet been described. Therefore, the successful design of P-chiral dicyclohexylammonium 2-(phosphoryl)acrylates in which the substituents at the phosphorus can have impact not only on the level but also on the mode of stereoselection became a challenging task. Access to the P-chiral acrylates of type **3** requires preliminary synthesis of the corresponding P-chiral phosphorylacetic acids. The number of P-chiral phosphorylacetates, which are accessible in enantiomerically pure form, is limited.[1,6]

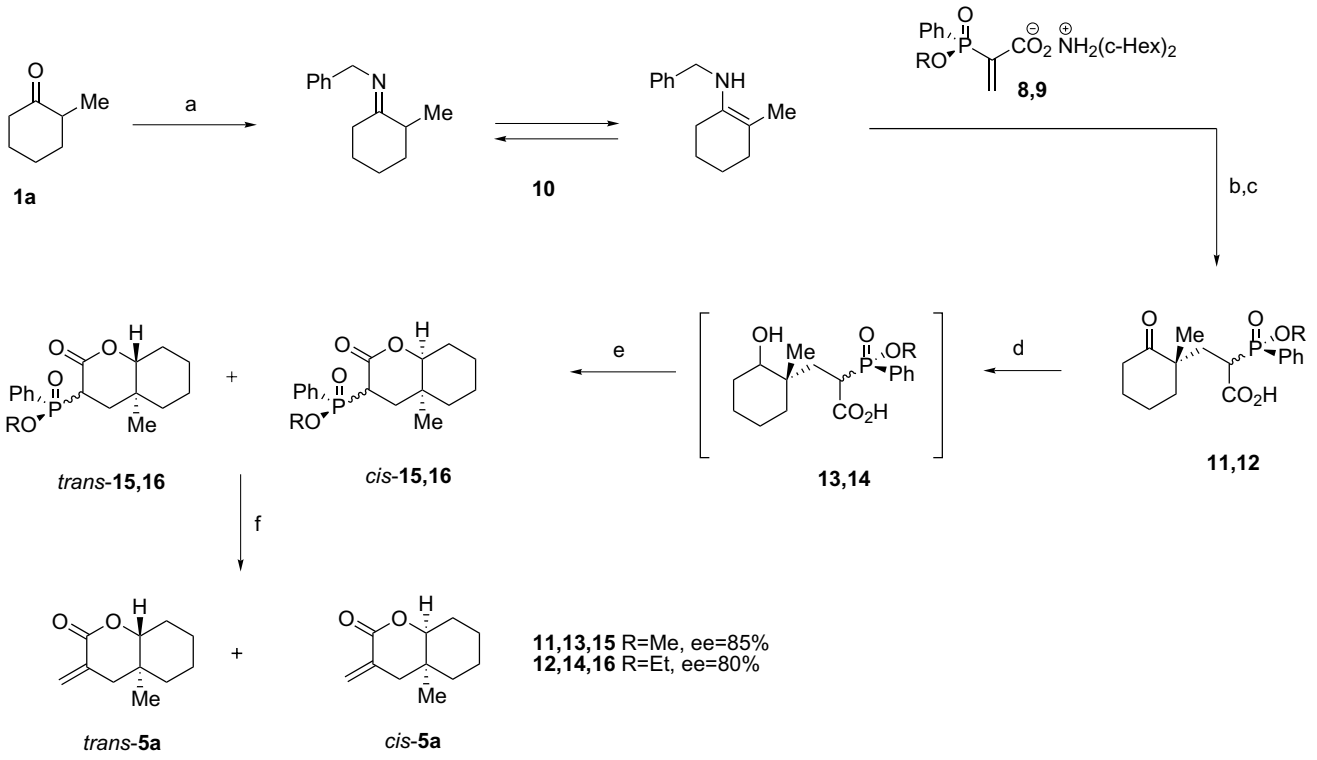
In our studies (*S*)-(−)-[methoxy(phenyl)phosphoryl]acetic acid **6** and (*S*)-(−)-[ethoxy(phenyl)phosphoryl]acetic acid **7**, introduced by Musierowicz in 1967, have served as the starting materials.[7] Herein we report on the synthesis of the P-chiral 2-(phosphinyl)acrylates **8** and **9** (Scheme 2) and the first example of their use as Michael acceptors with imine **10** (Scheme 3).

2. Results and discussion

The enatiomerically pure (*R*)-(−)-2-(phosphinyl)acrylates **8** and **9** were readily prepared from the corresponding (*S*)-(−)-phosphinylacetic acids **6** and **7** by the procedure previously reported for acrylate **3**.[8] Thus, dicyclohexylammonium salts of acids **6** and **7**, generated in situ, were reacted with an excess of paraformaldehyde (2 equiv) in boiling benzene in the presence of triethylamine, used in an equimolar amount with an azeotropic removal of water, to provide the corresponding acrylates **8** and **9** as white solids, each in 70% yield.[9]

The feasibility of our methodology was tested in the reaction of acrylates **8** and **9** with 2-methyl(benzylimino)cyclohexane **10**, derived from 2-methylcyclohexanone **1a** and benzylamine.[10] The addition reaction of imine **10** to acrylates **8** and **9** proceeded smoothly in benzene at room temperature. The complete consumption of salts **8** and **9** was observed after 2 days (^{31}P NMR). Ion-exchange chromatography of the crude Michael adducts gave 2-phosphinyl-5-oxoalkanoic acids **11** and **12**, each as an inseparable mixture of diastereoisomers. At this stage we were unable to determine the diastereoselectivity of the additions. The absolute configuration at the newly created quaternary stereocenter in acids **11** and **12** could be easily established by their transformation into α-methylene-δ-valerolactone **5a**. Acids **11** and **12** were converted to lactone **5a** by a standard procedure. The reduction of the carbonyl group was accomplished under mild conditions with KBH_4 in methanol. Lactonization of hydroxyacids **13** and **14** obtained was performed in toluene at room temperature in the presence of trifluoroacetic anhydride as a dehydrating agent[11] and α-(phosphinyl)lactones **15** and **16** were provided, each as an inseparable mixture of diastereoisomers. Finally, the HWE reaction of α-(phosphinyl)lactones **15** and **16** afforded α-methylene-δ-valerolactone **5a**. In each case, lactone **5a** was formed as a mixture of *trans*- and *cis*-diastereoisomers in a 1:2 ratio. This ratio reflects the degree of diastereoselection, which is attained by the reduction of oxoacids **11** and **12**.

The enantiomeric purity of lactone **5a** derived from acrylate **8** was higher (85% ee) than that obtained from acrylate



Scheme 3. Reagents and conditions: (a) benzylamine, *p*-TSA (cat), toluene, reflux, 24 h, 89%; (b) benzene, rt, 48 h; (c) Dowex 50 W, acetone/water, 79%; (d) MeOH, KBH_4 (2 equiv), rt, 24 h; (e) TFAA (1 equiv), toluene, rt, 24 h, 88%; (f) *t*-BuOK (1 equiv), $(HCHO)_n$ (5 equiv), Et_2O, rt, 1 h, 90%.

9 (80% ee), suggesting that the bulkiness of the alkoxy substituent of the stereogenic phosphorus atom is one of the factors determining the diasteroselectivity of addition. The absolute configuration of lactone **5a** was established by comparison of the chiral GC data with an authentic sample of **5a** prepared by the reported procedure.[4] This revealed that the products 4a(*S*),8a(*R*) *trans*-**5a** and 4a(*S*),8a(*S*) *cis*-**5a** are dominant stereoisomers for the additions as outlined in Scheme 3. Consequently, both acrylates **8** and **9** gave the same sense of stereoinduction and methoxyphosphoryl acrylate **8** ensured a higher diastereoselectivity as its ethoxy analogue **9**.

The chirality transfer observed must be the consequence of a transition state in which the phosphoryl group on the acrylate is arranged '*endo*' to the enamine (Fig. 1). Attack of the enamine then occurs with high selectivity from the *Re* face to give compounds **11** and **12**. The diastereoisomeric transition state resulting from the *Si* attack would be heavily hindered by interactions between the benzyl group on the enamine and the bulky phenyl group on the auxiliary.

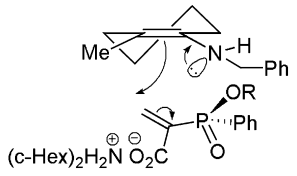


Figure 1.

3. Conclusions

In conclusion, we have developed a convenient method for the preparation of enantiomerically pure P-chiral dicyclohexylammonium 2-(phosphinyl)acrylates **8** and **9**. The utility of acrylates **8** and **9** was demonstrated in an asymmetric Michael reaction with imine **10**, which opened a new general route to the enantioselective synthesis of α-methylene-δ-valerolactones **5**.

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9. All new compounds gave satisfactory physical, analytical and spectroscopic data. Selected data for compound **8**: white crystals mp 136–138 °C; $[\alpha]_D = -14.1$ (*c* 0.57, $CHCl_3$); ^{31}P NMR ($CDCl_3$): δ 33.02; ^1H NMR ($CDCl_3$): δ 0.86–1.38 (m, 10H, $5 \times CH_2$), 1.55–1.71 (m, 6H, $3 \times CH_2$), 1.84–1.90 (m, 4H, $2 \times CH_2$), 2.79–2.88 (m, 2H, $2 \times CHN$), 3.67 (d, 3H, $^3J_{HP} = 11.0$, CH_3OP), 6.51 (dd, 1H, $^2J_{HH} = 2.5$, $^3J_{HP} = 18.7$, $=CH$), 6.83 (dd, 1H, $^2J_{HH} = 2.5$, $^3J_{HP} = 40.0$, $=CH$), 7.35–7.53 (m, 3H, $3 \times CH$), 7.85 (dd, 2H, $^3J_{HH} = 7.1$, $^3J_{HP} = 12.7$, $2 \times CH$); ^{13}C NMR ($CDCl_3$): δ 24.18 ($4 \times CH_2$), 24.49 ($2 \times CH_2$), 27.98 ($4 \times CH_2$), 50.11 (d, $^2J_{CP} = 6.1$, CH_3OP), 51.73 ($2 \times CHN$), 127.15 (d, $^3J_{CP} = 13.5$, $2 \times CH$), 130.79 (*C*H), 131.10 (d, $^2J_{CP} = 10.0$, $2 \times CH$), 131.44 (d, $^1J_{CP} = 139.2$, *C*P), 137.00 (d, $^2J_{CP} = 6.2$, $=CH_2$), 141.52 (d, $^1J_{CP} = 124.1$, $=CP$) 167.42 (d, $^2J_{CP} = 14.5$, *C*OO). Anal. Calcd for $C_{22}H_{34}NO_4P$: C, 64.85; H, 8.41; N 3.44. Found: C, 64.96; H, 8.33; N, 3.30. Compound **9**: white crystals mp 120–122 °C; $[\alpha]_D = -14.4$ (*c* 1.06, $CHCl_3$); ^{31}P NMR ($CDCl_3$): δ 30.93; ^1H NMR ($CDCl_3$): δ 0.95–1.38 (m, 10H, $5 \times CH_2$), 1.29 (t, 3H, $^3J_{HH} = 7.1$, CH_3CH_2OP), 1.56–1.71 (m, 6H,$3 \times CH_2$), 1.84–1.93 (m, 4H, $2 \times CH_2$), 2.74–2.85 (m, 2H, $2 \times CHN$), 3.92–4.15 (m, 2H, CH_2OP), 6.48 (dd, 1H, $^2J_{HH} = 2.6$, $^3J_{HP} = 18.7$, $=CH$), 6.83 (dd, $^2J_{HH} = 2.6$, $^3J_{HP} = 39.8$, $=CH$), 7.35–7.53 (m, 3H, $3 \times CH$), 7.84 (dd, 2H, $^3J_{HH} = 8.2$, $^2J_{HP} = 12.6$, $2 \times CH$); ^{13}C NMR ($CDCl_3$): δ 16.30 (d, $^3J_{CP} = 6.7$, CH_3CH_2OP), 24.62 ($4 \times CH_2$), 24.91 ($2 \times CH_2$), 28.52 ($4 \times CH_2$), 52.20 ($2 \times CHN$), 60.30 (d, $^2J_{CP} = 5.9$, CH_2OP), 127.48 (d, $^3J_{CP} = 13.2$, $2 \times CH$), 131.05 (*C*H), 131.38 (d, $^2J_{CP} = 10.1$, $2 \times CH$), 132.56 (d, $^1J_{CP} = 137.3$, *C*P), 137.48 (d, $^2J_{CP} = 6.9$, $=CH_2$), 142.14 (d, $^1J_{CP} = 124.11$, $=CP$), 167.98 (d, $^2J_{CP} = 13.9$, *C*OO). Anal. Calcd for $C_{23}H_{36}NO_4P$: C, 65.54; H, 8.61; N, 3.32. Found: C, 65.69; H, 8.53; N, 3.44.
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