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Study of syntheses and specific rotations of (*S*)-3-phenylhexan-3-ol and its derivatives

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Abstract—Tertiary alcohols, 3-phenylhexan-3-ol and 3-methylhexane-3-ol, and their derivatives were synthesized. The reaction conditions of the esterification of the tertiary alcohol with 2-NO_2PhCO_2Cl and 4-NO_2PhCO_2Cl were optimized. The absolute configuration of the derivative from (*S*)-3-phenylhexan-3-ol was identified by X-ray study and computational methods. Experimental results confirmed the computational specific rotation predictions by DFT-based and matrix methods.

1. Introduction

It is well known that specific rotation calculations for rigid chiral compounds can be obtained using quantum mechanics.[1–6] The computations of specific rotation for flexible, especially, linear stereogenic compounds are also reported.[7,8] However, due to the difficulty in searching for and computing most of the stable conformations in which the molecule can exist during specific rotation calculations of linear chiral compounds, successful examples are few when compared to those in rigid compounds. Recently, we reported a matrix method to predict the acyclic chiral secondary alcohols, amines and others.[9] This method can use less computation time to predict the specific rotation by use of the determinant value det(*D*) and k_0 values in a series of chiral compounds. Since the matrix method is still in its infancy, it needs a more standard chiral molecule for specific rotation computation tests. Chiral linear tertiary alcohols have rarely been tested before; we synthesized tertiary alcohols such as 3-phenylhexan-3-ol and its derivatives. By enantiomer separations, (*S*)- and (*R*)-3-phenylhexan-3-ols were obtained with almost 100% enantiomeric purity. X-ray experiments confirmed the absolute configuration of (*S*)-3-phenylhexan-3-ol by converting (*S*)-3-phenylhexan-3-ol into an amide derivative, which had a standard (*S*)-configuration. The syntheses of (*S*)-3-phenylhexan-3-ol, derivatives and specific rotation computations are reported herein.

2. Results and discussion

2.1. Syntheses and identifications of (*S*)-3-phenylhexan-3-ol and its derivatives

Synthetic routes to (*S*)-3-phenylhexan-3-ol and its derivatives are illustrated below.[10–13] The esterification of tertiary alcohol is generally very difficult due to the big repulsive effect among the groups. For example, if the tertiary alcohol was obtained after the addition of PhMgBr to the ketone **3**, and this tertiary alcohol was then used to esterify with 4-NO_2–PhCOCl, then the yield of ester **4** would be very low or no ester product would be obtained. The reaction products were also too many to be separated. After a series of experiments using different solvents and temperatures, continuing a reaction conditions were found to be efficient for the conversion of **3** to **4**. In this esterification, the chloride must be added at the low temperature, −76 °C, after the addition of PhMgBr to ketone **3** and then kept for over 4 h. Resolution of the enantiomers, (*R*)- and (*S*)-**4**, was tried using Chiralcel OD-H and Chiralcel OB columns. Only Chiralcel OD-H was able to separate the enantiomers. The effect of the substituents on the benzoate on the chiral separation is very big. For example, if the –NO_2 was not reduced to –NH_2, no column could separate

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the enantiomers. The position of the $-NO_2$ or $-NH_2$ also had the effect on chiral separation. Esterification of 2-NO_2–PhCOCl with the alcohol afforded the 2-NO_2 analogue ester. However, these two enantio-2-NO_2 analogue esters, or their reduced enantio-amines, could not be separated by either Chiralcel OD-H or Chiralcel OB.

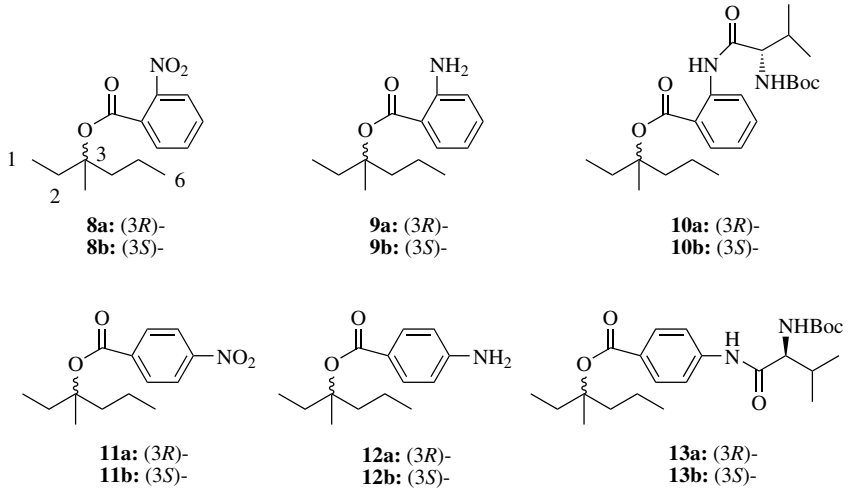
Enantiomer (*S*)-**4** was hydrolyzed to the chiral tertiary alcohol **5**. The specific rotation of **5** was +11.6 deg/[g/mL] (*c* 0.00805, >99% ee HPLC purity) determined in chloroform at room temperature.

Control of the pH was required during the reduction of (*S*)-**4** to (*S*)-**6**. The hydrolysis of the ester was fast at pH < 5.0 whereas the $-NO_2$ was reduced to $-NH_2$. No amount of amine (*S*)-**6** was formed after the reduction. Once the pH value was over 7, the reduction reaction was not finished and even the reaction time was increased to two days. Thus, a suitable pH value for the reduction was 6.

Amine (*S*)-**6** was then reacted with (*S*)-2-(*tert*-butoxycarbonylamino)-4-methylpentanoic acid to afford amide **7** with a dual-chiral-center. The condensation reagent, CDMT or NMM, was normally required in the reaction, and most of the time, either of them was enough to remove the water formed in the condensation reaction. However, in this condensation reaction, one mole of CDMT and three moles of NMM were necessary for one mole of **6**. When either CDMT or NMM was used in the condensation, it afforded a very low yield of amide **7** (less than 10% yield).

Solvents for crystal formation were optimized using methanol, acetone, ethyl acetate, *n*-hexane and their mixtures with different combinations and different ratios. The suitable solvents were a mixture of *n*-hexane/ethyl acetate (2:1, v/v). The re-crystallization temperature was 3–5 °C in a refrigerator. The crystals were then selected for X-ray experiments, the X-ray structure is illustrated below. Since the absolute configuration at C2B (in the chiral amino acid section) was already known as (*S*), which meant that once the whole molecule was pictured by X-ray, then, the carbon C3A that connected with an aromatic ester could be directly configured. The X-ray experiment confirmed that carbon (C3A) had an (*S*)-configuration (Fig. 1).

Not every chiral compound could be separated in this way. Another tertiary alcohol, 3-methylhexan-3-ol, was synthesized using a similar route in Scheme 1, and this tertiary alcohol was then converted into the corresponding esters and others. The structures of compounds **8** to **13** are illustrated below. Enantiomers **8a** and **8b** could not be separated by both chiral columns. The enantiomers of **9**, **9a** and **9b** could be separated using Chiralcel OD-H. However, enantiomers **9a** and **9b** decomposed to other complex mixtures during the purification. To obtain more stable isomers, compound **9** was converted into **10**. Unfortunately, **10a** and **10b** could not be separated. Thus, 3-methylhexan-3-ol was then converted into **11**–**13**. However, none of these could be separated by Chiralcel OD-H or OB-H columns. The trial was attempted to use L-tartaric acid to react with one enantiomer of amines **9** or **12** to form the corresponding crystal, respectively. Unfortunately, no crystal was formed using different solvents, such as alcohols, ethyl acetate, diether or their mixtures.



8a: (3*R*)-
8b: (3*S*)-

9a: (3*R*)-
9b: (3*S*)-

10a: (3*R*)-
10b: (3*S*)-

11a: (3*R*)-
11b: (3*S*)-

12a: (3*R*)-
12b: (3*S*)-

13a: (3*R*)-
13b: (3*S*)-

Most chiral compounds have specific rotation values that can be easily obtained. Therefore, it is useful to use a specific rotation value to determine the absolute configuration. It is very important for researchers to use this method in their practices, and this has led to the use of theoretical methods.

2.2. QM model

The first example of using Hartree–Fork theory to calculate the specific rotation was reported by Polavarapu in 1997.[2a,b,e] Stephens et al. studied the DFT-based specific rotation computations;[2c,d,3d,4b,c,5a–c] Ruud,[3a–c,4b,6c,7b,c] Crawford,[1a,b,e] Pederson[3e,f] and Koch[1b,3e,f] reported coupled-cluster (CC) methods; while Wiberg et al.,[4a,8a] Coriani et al.[7b,c] reported many valuable data for specific rotation calculations. Over the past decade, Wipf et al.,[1c,d,8b] Helgaker,[3a,c] Grimme,[7a] Giorgio[4d] and other chemists[6b,c] explored several computational approaches for use in specific rotation calculations. Studies related to conformation-

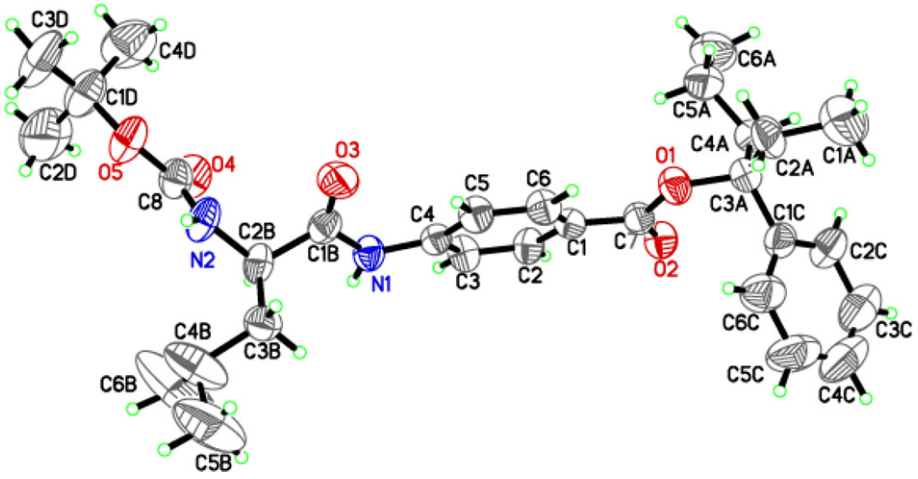
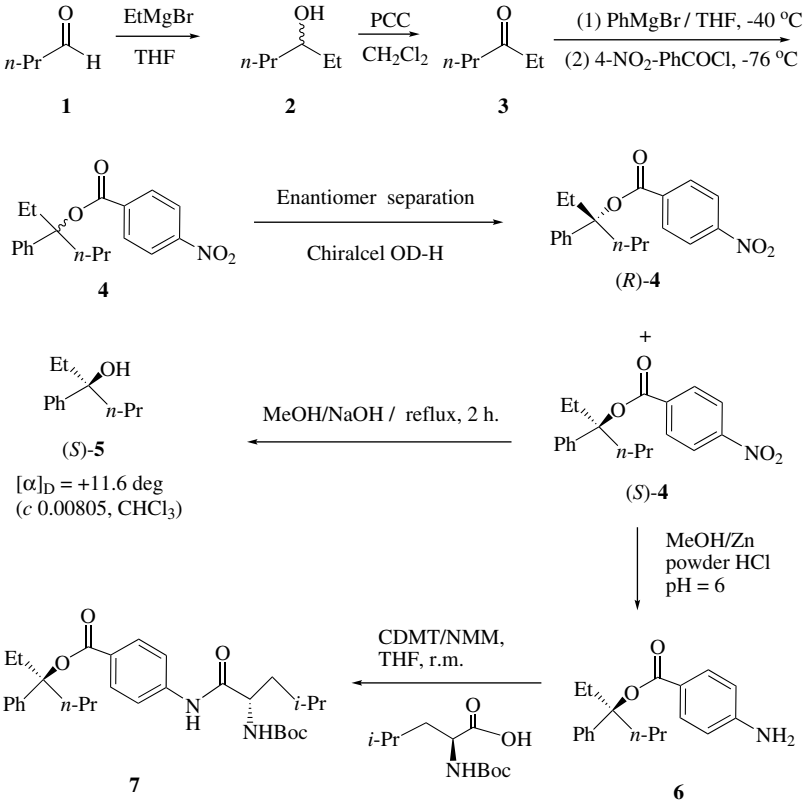


Figure 1. The X-ray structure for (*S*)-3-phenylhexan-3-yl 4-((*S*)-2-(*tert*-butoxycarbonylamino)-4-methylpentanamido) benzoate, **7**.



Scheme 1. The synthetic routes to 3-phenylhexan-3-ol and its derivatives.

ally flexible molecular specific rotation were also reported.[4a,7a,b,8a,b] Quantum mechanical theory relates specific rotation to the following formula:

$$[\alpha]_v = \frac{28\,800\pi^2 N_A v^2}{c^2 M}\gamma_{s,v}[\beta(v)]_0 \qquad (1)$$

where N_A is Avogadro's number, M is the molecular weight, c is the light speed in vacuum, γ is the correction from solvent which is either neglected ($\gamma = 1$) or approximated by equation: $\gamma = (n^2 + 2)/3$. $[\beta(v)]_0$ is the value of $\beta(v)$ at the gas-phase equilibrium geometry, in which $\beta(v)$ is the frequency-dependent electric dipole–magnetic dipole polarizability of molecule. Thus, the value of $[\alpha]_v$ depends upon the magnitude of the tensor of $[\beta(v)]_0$.

For a chiral molecule with one or more stable conformations with close energy, all the conformational specific rotation values should be calculated. Finally, these magnitudes can be summed up by using the Boltzmann formula. The calculated values are the absolute specific rotation value for this chiral molecule.

2.3. Matrix model

In our recently reported matrix model, which described four substituents surrounding a stereogenic center,[9] four substituents' variables, comprehensive mass (**m**), radius (**r**), electronegativity ($\boldsymbol{\chi}$) and symmetry (**s**) were used in a matrix **F** function. If an atom is directly connected to the stereogenic center, its coefficient is b_1. Coefficients of the other atoms, which are further removed, are b_2, b_3, and so on. Thus, the comprehensive mass of the substituent group becomes

$$\mathbf{m} = b_1 m_1 + \Sigma b_2 m_2 + \Sigma b_3 m_3 + \Sigma b_4 m_4 + \cdots$$

Here m_1 is the mass of atom 1, which is directly connected to the stereogenic center, and m_2 is the mass of atom 2, which is directly bound to atom 1. Since more than one atom can be bonded to atom 1, the summation term is used to indicate that the contributions of all these atoms must be included. If one substituent has the highest symmetry operation number N, and this symmetric axis passes through the atom which is connected to the stereogenic atom, then the symmetry factor for that substituent is **s** ($\mathbf{s} = [(N-1)/N]^2$). It was proposed that the determinant value (det(D)) is proportional to the specific rotation magnitudes for this chiral molecule. The matrix method gave a relative value for chiral molecule which requires us to use both det(D) and k_0 values to characterize the prediction. This matrix method was also extended to a dual-chirality molecular specific rotation computation.[10]

The effects of temperature, solvent, and frequency of light on a specific conformational specific rotation are the functions $f(t)$, $f(s)$, and $f(v)$. When these factors were held constant in a specific rotation determination, the overall contributions to the specific rotations for the ith conformation could be represented by function $\mathbf{F}_{\mathrm{con}i}$.

$$\mathbf{F}_{\mathrm{con}i} = \mathrm{k}\begin{bmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{bmatrix}\begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{bmatrix} \quad (2)$$

where k is the sum of all the constants (e.g., $k_1 + k_2 + k_3 \cdots$). $k_1 = f(v)$, $k_2 = f(s)$, $k_3 = f(t), \cdots$

The total contribution **F** from all the conformations can be written in the form of the Boltzmann distribution

$$\mathbf{F} = \Sigma(\mathbf{F}_{\mathrm{con}i})(\mathrm{Q}_i/\Sigma\mathrm{Q}_i) \quad (3)$$

where $Q_i = k\exp(-\Delta G_i/RT)$, Q_i is the amount of the ith conformation, k and S are constants, ΔG_i is the difference between ith conformation's free energy and the lowest conformational free energy.

The coefficients, a_1, a_2, a_3, and a_4 were unknown and the specific functions of $f(t)$, $f(s)$, and $f(v)$ were also unknown. However, they are constant when light frequency and temperature are fixed. Thus, we can study the middle matrix. Since a matrix is not a scalar number, we defined the determinant of the matrix as det(D), which is proportional to the specific rotation values, and this is the relative specific rotation value. Also, the sodium D line is used to obtain the specific rotation. As a result, one conformation has

$$[\alpha]_{\mathrm{D}i} = k \times a_1 \times a_2 \times a_3 \times a_4 \times \det(D_i) = k_0 \times \det(D_i) \quad (4)$$

where

$$\det(D_i) = \begin{vmatrix} \mathbf{m}_1 & \mathbf{r}_1 & \boldsymbol{\chi}_1 & \mathbf{s}_1 \\ \mathbf{m}_2 & \mathbf{r}_2 & \boldsymbol{\chi}_2 & \mathbf{s}_2 \\ \mathbf{m}_3 & \mathbf{r}_3 & \boldsymbol{\chi}_3 & \mathbf{s}_3 \\ \mathbf{m}_4 & \mathbf{r}_4 & \boldsymbol{\chi}_4 & \mathbf{s}_4 \end{vmatrix} \quad (5)$$

The different conformations of the chiral molecule have different energies. Thus, the final observed specific rotation must employ the Boltzmann distribution of all these conformations.

$$\det(D) = \Sigma(\det(D_i))(Q_i/\Sigma Q_i)$$
$$[\alpha]_{\mathrm{D}} = k_0 \times \det(D) \quad (6)$$

As mentioned above, it is impossible to obtain a_1, a_2, a_3, and a_4 and k values at this stage. Therefore, there is no absolute value to [α]. However, it is useful to obtain the relative values by computing det(D) since det(D) is the initial characteristic of that molecule and is proportional to the specific rotation values when the outside factors are held in a constant. It needs to use both det(D) and k_0 values to characterize the specific rotation prediction using Eq. (6). In our previous report,[9] the effect of the different conformations on the specific rotation in the QM method was converted into the effect of different radius values on the det(D) magnitude in a matrix model. In a series of chiral compounds, the recorded specific rotation values were proportional to their det(D) values.

Our previously reported quantum method[7a] was used for specific rotation calculations first via a GAUSSIAN 03 package.[14] Alternatively, (*S*)-3-phenylhexan-3-ol was selected for conformational searches, optimizations and specific rotation computations before experiments. In total, 119 conformations of (*S*)-3-phenylhexan-3-ol within the energy window of 0–5 kcal/mol were found from over 400 stable conformations, which were obtained using an AM1 force field via HYPERCHEM package, when the lowest conformational energy was used as the reference zero-point. The selected 119 conformations were then selected for optimizations at the B3LYP/3-21G* level. There were 22 low energy conformations (energies from 0 to 3 kcal/mol) found from these 119 B3LYP/3-21G(d)-optimized geometries, and they were selected for further optimization at the B3LYP/6-31G(d) level. Finally, a total of 11 conformations, whose energies were in the window of 0–2.0 kcal/mol, were used in specific rotation calculations at the B3LYP/aug-cc-pVDZ and B3PW91/aug-cc-pVDZ levels, respectively. The 11 conformations were further optimized at the MP2/6-31+G* level, and these 11 MP2/6-31+G*-optimized conformations were used in specific rotation computations at the B3LYP/aug-cc-pVDZ and B3PW91/aug-cc-pVDZ levels, respectively, again. The energetics after zero-point energy (ZPE) correction, free energy and totally electronic energy were used in the Boltzmann sums for whole

Table 1. The calculated specific rotation for (*S*)-3-phenylhexan-3-ol using four methods

	$[\alpha]_E$[a]	$[\alpha]_{E^0}$[b]	$[\alpha]_G$[c]	$[\alpha]_{CHCl_3}$
Method A	+2.8	+3.2	+4.4	+2.9
Method B	−1.2	−13.0	−12.3	−1.0
Method C	+2.7	+3.1	+1.6	+2.8
Method D	−1.3	−12.9	−12.2	−1.2

[a] The total electronic energy data at the B3LYP/aug-cc-pVDZ level were used in the specific rotation computations in methods A and B, and at the B3PW91/aug-cc-pVDZ level in methods C and D.
[b] Energetics after the zero-point energy correction at the B3LYP/6-31G(d) level in methods A and C, or at the MP2/6-31+G(d) level in methods B and D, were used.
[c] The free energy data at the B3LYP/6-31G(d) level in methods A and C or at the MP2/6-31+G(d) level in methods B and D were used.

Table 2. The calculated specific rotation for (*S*)-3-phenylhexan-3-ol using full optimized geometries in chloroform via the PCM model

	$[\alpha]_E$[a]	$[\alpha]_{E'}$[b]	$[\alpha]_G$[c]
Method E	+2.2	+3.1	+2.3
Method F	−9.3	−8.5	−6.2
Method G	+2.0	+2.7	+0.7
Method H	−9.5	−8.4	−7.3

[a] The total electronic energy data at the B3LYP/aug-cc-pVDZ were used in methods E and F in the specific rotation computations, and those at the B3PW91/aug-cc-pVDZ level were used in methods G and H.
[b] The total electronic energy data at the MP2/6-31+G(d) level used.
[c] The total free energy in solution at the MP2/6-31+G(d) level were used.

molecular specific rotation calculations. Here, method A means that the B3LYP/6-31G(d)-optimized geometries in the gas phase were used in specific rotation calculations (B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)), method B means that the MP2/6-31+G(d)-optimized conformations were used in specific rotation computations (B3LYP/aug-cc-pVDZ//MP2/6-31+G(d)). In methods C and D, B3PW91/aug-cc-pVDZ//B3LYP/6-31G(d) and B3PW91/aug-cc-pVDZ//MP2/6-31+G(d) were used in the specific rotation predictions. (*S*)-3-Phenylhexan-3-ol was predicted to have +1.3 to 1.9 values via methods A and C (Table 1), or −2.3 to −13.0 by methods B and D. Indeed, chiral tertiary alcohol **5** has an (*S*)-configuration with a value of +11.6. DFT-optimized geometries provided a more correct prediction of (*S*)-**5** specific rotation (methods A and C) instead of MP2-optimized geometries (methods B and D). This is unexpected. The reason might be that the solvent effect on the specific rotation values was not investigated in the specific rotation calculations.

The effect of solvent could have a big effect on the specific rotation values or even change the sign of specific rotation. Thus, the effect of chloroform on specific rotation ($[\alpha]_{CHCl_3}$) was investigated. Single point energy (SPE) calculations for both B3LYP/6-31G(d)- and MP2/6-31+G(d)-optimized geometries were first performed at the B3LYP/6-311+G(d,p) level in chloroform using PCM model (Table 1). The SPE was used to correct the specific rotation values in solvent chloroform (d,p) level in chloroform using PCM model (Table 1). However, it did not change the specific rotation direction (the sign of specific rotation) in this way.

The effect of the geometries had a big effect on the specific rotation values, and the effect of solvent on the geometries was also large as reported in Coriani's study.[7c] The geometries used in methods A and B were obtained in the gas phase, the structures of the different conformations could be different from those in solution. This could be the reason that the computed specific rotations using methods A to D did not give the expected predictions. Thus, optimizations of the conformations in chloroform were performed at the B3LYP/6-31G(d) and MP2/6-31+G(d) levels, respectively, using a PCM model. The geometries obtained were then used for specific rotation computations again at the B3LYP/aug-cc-pVDZ and B3PW91/aug-cc-pVDZ levels, respectively. Four methods E to H were applied to the specific rotation computations: method E, B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)-$CHCl_3$; method F, B3LYP/aug-cc-pVDZ//MP2/6-31+G(d)-$CHCl_3$; method G, B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)-$CHCl_3$; and method H, B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d)-$CHCl_3$. The results are listed in Table 2. The calculated specific rotation magnitudes obtained at the B3LYP/aug-cc-pVDZ level were about 3 using the fully B3LYP/6-31G(d)-optimized geometries in chloroform via PCM model (methods E and G, Table 2). The specific rotation values became about −5.7 to −9.0 when the full MP2/6-31+G(d)-optimized structures in chloroform were used in specific rotation computations (methods F and H, Table 2).

The DFT theory (methods A and E) predicted the specific rotation sign direction correctly although the absolute specific rotation values were a little lower than the recorded magnitudes. MP2 theory (methods B and F) predicted the wrong specific rotation direction. However, the absolute values approached the experimental one. Indeed, it is necessary to use the sign of the specific rotation magnitudes to judge the absolute configuration. Thus, in this example, although the computational times in methods B and F were much longer than those in methods A and E, the correct prediction of the configuration is obtained using methods A and E. This is an unexpected result. However, this does not mean that the high computational method is less valuable. Indeed, the selection of the computational method and the basis set in calculation could have a great influence on the results of the specific rotations.[7b] This is similar to what Crawford reported that 'in spite of these advances, it is not yet understood what level of theory is necessary to obtain 'the right answer for the right reason' for specific rotation, and many successes rely implicitly on fortuitous cancellation of errors (e.g., limited basis sets, lack of explicit solvation, and vibrational averaging).[1a] It is possible to find a suitable QM method to give good predictions for the linear chiral molecular specific rotation values, including compound **5** in this research, although this is time-consuming.

It would be time-consuming to compute the specific rotations for linear chiral molecules if to use the above methods A to H, since the numbers of stable conformations with low energy were huge. Once the stable conformation numbers were over a hundred obtained at the B3LYP/6-31G(d), the specific rotation prediction for a linear chiral

molecule would be expensive. For example, compounds **4** or **7** in Scheme 1 were very flexible. The number of stable conformations, which had an energy of 0–5 kcal/mol, and needed to be re-optimized at the B3LYP/3-21G(d) level were over 2000 and 8000, respectively, after the conformational search using AM1 force field via the HYPERCHEM package. The stable conformations needed to be optimized at the B3LYP/6-31G* level would be over hundreds and thousands, respectively, for **4** and **7**. Thus, to use any one of methods A to H to predict the specific rotations of **4** and **7** would be very time-consuming. If a computer's computational rate is fast enough, this is still a good choice to calculate specific rotations for linear chiral molecules as **4** and **7**. However, if there is another method to do the predictions of specific rotation for linear chiral molecules, such as **4** and **7**, it would prove to be helpful. The matrix method provides another choice to do the predictions of specific rotation for **4** and **7**.[9] Matrix model is deduced from mathematical theory, and is different from the quantum theory. The parameters used at the present time were calculated from the standard molecular structures. For example, the bond length of C–C was regarded as 1.54 Å, the angle sp^3 hybridized carbon was 108°, and so on. These parameters were used in the specific rotation predictions for the reported 94 chiral acyclic compounds, and it worked well via the combination with k_0.[9] The same series of chiral compounds had similar constant k_0 values as mentioned in the matrix model section.

The matrix method predicted the specific rotation by using the det(D) and k_0 values. In a similar series of chiral compounds, the k_0 values should be constant. By computing the det(D) for the target chiral molecule and to use the k_0 value of target molecular analogue, the specific rotation could be predicted for the target chiral molecule. Thus, matrix method was used to calculate the k_0 for (*S*)-3-phenylhexan-3-ol, **5**. The magnitudes of **m**, **r**, **χ**, and **s** for substituents in **5** were selected directly from our recent report. [9] The determinant det(D) was −0.42. Thus, the k_0 value was −27.6 ($k_{0,5} = 11.6/(-0.42)$). The specific rotation value could be measured in different solvents, various k_0 for different solvents could be obtained.

As mentioned above, it is possible to use this $k_{0,5}$ to predict the specific rotation values of chiral **4**. The calculated determinant value for chiral compound **4** is −0.07. This value of −0.07 predicted that its specific rotation value should be +1.9 in chloroform using $k_{0,5}$ (−27.6) value via Eq. (5) since **4** is the tertiary ester derived from **5**. The determined specific rotation for chiral compound **4** is +1.6 (*c* 0.026, $CHCl_3$). As can be seen, this value is close to the prediction of 1.9. Its experimental k_0 is −22.9 ($k_{0,4}$).

The specific rotation for **7** was predicted using this method too. Compound **7** has two kinds of stereogenic centers, one center has a proton, whose det(D) value was +0.05; another has not proton and its det(D) magnitude was +2.16. The sum of the two det(D) values was 2.21. The size of **7** is more close to that of **4** instead of **5**. Thus, the $k_{0,4}$ (−22.9) was used for the prediction of a specific rotation of **7**. The calculated specific rotation for **7** was −50.6 ($2.21 \times (-22.9) = -50.6$) in chloroform. The recorded specific rotation is −33.3 (*c* 0.01485, $CHCl_3$). Its experimental $k_{0,7}$ is −15.1.

3. Conclusion

The quantum methods to predict the specific rotation values for acyclic chiral compounds proved to be difficult since the number of stable conformations is very large. The longer the carbon chain in the acyclic chiral compound, is the more the numbers of the stable conformations would be. The specific rotation computations for these large acyclic compounds would be time-consuming although the predictions match the experimental results. Relatively, matrix method could provide an additional method in the specific rotation predictions for these acyclic chiral compounds. This is another mathematic method to predict specific rotation values for tertiary alcohol derivatives; these derivatives require one of the four substituents which are connected to the stereogenic center (one of the **s** values in det(D) is not equal to zero).

4. Experimental

A Brucker-AV-400 instrument was used for NMR determinations using $CDCl_3$ as the solvent unless another solvent is specifically stated. The chemicals were used as received. A Waters model 2695 high pressure liquid chromatography instrument was used for HPLC analyses and chiral separations. Thermometers used in the reaction temperature determinations were not corrected. Silica gel (200–400 mesh) was used. Chiralcel-OD-H column was used in the analysis and separation for compound **4**. The procedures for the formations of compounds **4** to **7** are described below.

4.1. 3-Phenylhexan-3-yl-4-nitrobenzoate, 4

A 250 mL three-necked round-bottomed flask equipped with a magnetic stirbar and reflux condenser was flushed with nitrogen, and charged with 50 mL anhydrous THF and 800 mg (8 mmol) of **3**. A solution of phenylmagnesium bromide (2.7 mL, 3 M, 8.1 mmol) was added dropwise over a period of 0.5 h at −30 °C, the solution was then warmed to 50 °C for 10 min. The reaction mixture was cooled down to −78 °C, and a solution of 4-NO_2–PhCOCl (8 mmol in 5 mL THF) was added dropwise into the flask over a period of 10 min and kept for 20 min. After being stirred overnight at room temperature, the solution was treated with 2 mL water and extracted with EtOAc (6 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (1:20 EtOAc/hexanes) to afford **4** as a yellow liquid (1.3 g, 50% yield), which solidified slowly to give a pale yellow product. Chiral separation of **4** was carried out by HPLC using Chiralcel-OD-H column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.80 (m, 3H), 0.87–0.91(m, 3H), 1.17–1.21 (m, 2H), 2.24–2.34 (m, 2H), 2.48–2.60 (m, 2H), 7.28–7.41 (m, 5H), 8.27 (dd, $J = 6.8$ Hz, 2.0 Hz, 2H), 8.34 (dd, $J = 6.8$ Hz, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 7.7, 14.1,

16.6, 30.5, 39.6, 89.8, 123.5, 125.0, 127.0, 128.2, 130.5, 136.8, 143.0, 150.4, 162.9.

4.2. (*R*)-3-Pheny-3-hexanol, 5

To an aqueous solution of KOH (220 mg, 4 mmol, 7 mL) was added the solution of methanol (3 mL) and lithium chloride (168 mg, 4 mmol), and then **4a** was added (53 mg, 0.16 mmol). The mixture was refluxed for 2 h and diluted with water. The solution was extracted with diethyl ether (6×25 mL). The combined organic phase was washed with brine (3×5 mL), dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure. The residue was purified by column chromatography (1:20 EtOAc/hexanes) to give **5** as a colorless oil (21.5 mg, 75% yield). ^{1}H NMR ($CDCl_3$), δ 0.73–0.76 (m, 3H), 0.83–0.86 (m, 3H), 1.01–1.11 (m, 1H), 1.28–1.30 (m, 1H), 1.75–1.89 (m, 4H), 7.19–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$), δ 7.7, 14.4, 16.7, 35.2, 44.8, 77.2, 125.2, 126.1, 127.9, 146.0.

4.3. 3-Phenylhexan-3-yl-4-aminobenzoate, 6

To a suspension of Zn powder (800 mg) in a mixture of methanol (20 mL) and water (2 mL) was added **4a** (200 mg, 0.6 mmol), then 3 M HCl was added dropwise into the mixture and the pH value was carefully controlled at 6.0. The suspension was stirred at ambient temperature for about 50 h until TLC analysis indicated the complete conversion of **4a** to **6**. The mixture was filtered and the solution was washed with 10 mL brine and dried over Na_2SO_4 (anhydrous). Evaporation of the solvent afforded **6** (160 mg, 90% yield) as a yellow oil without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82–0.86 (m, 3H), 0.92–0.96 (m, 3H), 1.18–1.31 (m, 1H), 1.32–1.36 (m, 1H), 2.22–2.33 (m, 2H), 2.56–2.65 (m, 2H), 4.15 (br, 2H), 6.77 (dd, $J = 6.8$ Hz, 1.6 Hz, 2H), 7.33–7.52 (m, 5H), 8.02 (dd, $J = 6.8$ Hz, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 7.7, 14.2, 16.6, 31.0, 40.2, 87.4, 113.7, 121.1, 125.1, 126.5, 127.9, 131.5, 144.2, 150.6, 165.0.

4.4. Compound 7

To a solution of Boc-L-leucine (64 mg, 0.3 mmol) in THF (8 mL), at room temperature, were added 55 mg (0.3 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-trizaine (CDMT) and 90 mg (0.9 mmol) of *N*-methylmorpholine (NMM). After a white precipitate formed, a solution of amine **6** (80 mg, 0.3 mmol) was added into the flask. The mixture was stirred overnight and then quenched with 0.5 mL water. The solution was then extracted with EtOAc (5×15 mL). The combined organic phases were washed successively with saturated sodium carbonate, water, 1 M HCl, water, and brine, respectively. The organic layer was dried and subjected to silica gel chromatography (1:6 EtOAc/hexanes) to give **7** as a colorless solid (65 mg, 42.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70–0.73 (m, 3H), 0.81–0.84 (m, 3H), 0.93–0.96 (m, 6H), 1.11–1.28 (m, 2H), 1.43 (s, 9H), 1.71–1.75 (m, 3H), 2.17–2.22 (m, 2H), 2.50–2.51 (m, 2H), 4.41 (m, 1H), 5.46 (d, $J = 5.2$ Hz, 1H), 7.22–7.39 (m, 5H), 7.61 (d, $J = 6.8$ Hz, 2H), 7.98 (d, $J = 6.8$ Hz, 2H), 9.31(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 14.1, 16.5, 22.9, 24.6, 28.8, 30.6, 40.0, 40.7, 53.8, 80.5, 88.0, 118.8, 125.0, 126.5, 126.6, 127.9, 130.5, 142.0, 143.7, 156.6, 164.3, 171.8. CCDC No. 680024.

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