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BIOCHEMICAL ASYMMETRIC REDUCTION OF PROCHIRAL KETONES BY BIOCATALYSIS USING DAGLA BAIDA *(PHOENIX DACTYLIFERA L)*, FRUIT GROWN IN SOUTH OASES OF ALGERIA

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ABSTRACT

The asymmetric biochemical reduction of prochiral ketones produces optically secondary alcohols which are important in synthesis as intermediate compounds in the biological and medical field. This is done using chemical and biochemical catalysts but the latter attracted much attention because of the low cost, high efficiency and special selectivity for its environmental friendliness and its contribution to certain recommended green chemistry principles. Our aim in this research was to contribute to this area by using biochemical catalysts with plant sources that develop the oases of southern Algeria such as the fruits of the dagla baida *(Phoenix dactylifera L)* by different states (Fresh, Juice, dry powder**).** The acetophenone and 4'-haloacetophenones (X = F, Cl, and Br) were chosen as typical ketones and the yield was (40-78%) and optical purity (50-96%). The obtained results indicate that the white dactylifera fruits can be used as biochemical catalysts to contribute to the preparation of many pharmaceutical compounds.

KEYWORDS: dagla baida, Phoenix dactylifera L, biocatalyst, asymmetric reduction, chiral alcohols.

I. INTRODUCTION

The trend towards achieving and applying the principles of green chemistry for the safety of the environment and reducing the dangers of chemicals has recently become among the concerns of chemists. Many of the plants and vegetables were used as biochemical catalysts in organic preparation instead of chemicals such as *(Cynara scolymus L, Terfezia sp and Phoenix dactylifera L)* medlar fruit *(Mespilus germanica L)* [i-iii] and other enzymatic catalysts with plant sources [iv-v], particularly in the non-homogeneous reduction of ketones, which is considered to be one of the most important fundamental reactions to the production of clear alcohols used in many areas such as pharmaceuticals and agrochemical.

In recent years, these interactions with plant-based enzymes have generated a great deal of interest in their vast biotechnological potential[vi-viii]. Some of the important features of these biomarkers are their low cost, high versatility and efficiency, as well as highly desirable chemical aspects such as chemical fusion what made the biochemical reactions very attractive for the industrial sector [ix].

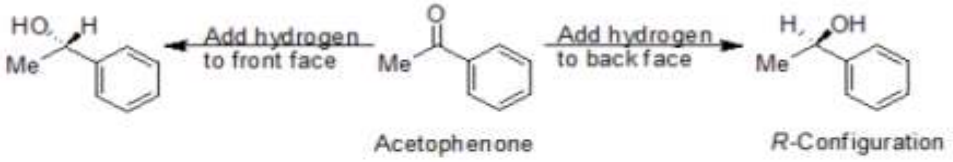
The biocatalytic transformations using plants can be applied in bioreduction of ketones [x], enzymatic lactonization [xi], hydrolysis of esters [xii], addition of hydrogen cyanide [xiii], and hydroxylation and oxidation reaction [xiv]. The biocatalysts used for the asymmetric reductions, baker's yeast [xv-xix], and vegetables [xx], germinated plant [iv] has been applied to organic synthesis because these biocatalysts are easily obtainable from markets and easily manipulated. An increasing number of reports dealing with the assessment of bioreduction of prochiral ketones using plants are frequently available [xxi-xiv].

Our aim in this research was to contribute to this area by using biochemical catalysts with plant sources that develop the oases of southern Algeria such as the fruits of the dagla baida *(Phoenix dactylifera L*) in **(scheme1),** The acetophenone and 4'-haloacetophenones (X = F, Cl, and Br) were chosen as typical ketones

scheme1: fruits of the dagla baida

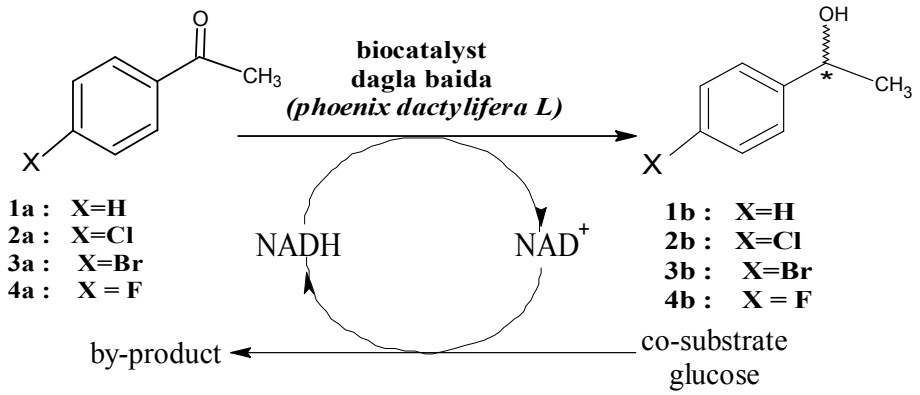
II. RESULTS AND DISCUSSION

Asymmetric transformations invariably involve the conversion of two dimentional substrate into a three dimentional product. For prochiral ketones such as acetophenone reduction shown in (**scheme- 2)**, addition to the back face gives 1-phenyl alcohol with R configuration, while addition to the back face gives alcohol with S configuration. The problem of course is that most common reducing agents, such as sodium borohydride or lithium aluminum hydride, react equally readily with either face. The most obvious solution to this problem is to use a hydride source which itself is enantiomerically pure in principal such as reagent will transfer the hydride to each face of the ketone through diastereoisomerically distinct transition state, which gives at least a fighting chance of an energy difference, and preference for addition to one face over the other.



scheme 2

Moreover, plants are potential biocatalysts used as the alternative solution to this problem, since they are easily obtainable from markets and easily manipulated. Asymmetric reduction reactions of acetophenone **1a**, 4-chloroacetophenone **2a**, 4'- bromoacetophenone **3a**, 4'-fluoroacetophenone **4a** and by the fruits of the dagla baida *(Phoenix dactylifera L***)** was investigated **(Scheme-3).**



Scheme 3

III. EXPERIMENTAL

III.1 General Methods

Acetophenone **1a**, 4'-chloroacetophenone **2a**, 4'-bromooroacetophenone **3a**, and 4'-fluoroacetophenone **4a**, were purchased from Aldrich. These chemicals were used without further purification. Thin-chromatography (TLC) was performed using precoated plates (Aluminium foil, silica gel 60 F254 Merck, 0.25mm). Merck 60 silica gel (230-400 mesh) was used for flash chromatography. Optical rotations were determined on Euromex Polarimeter PM. 5400 (Mitscherlich type polarimeter).

All 400.15 MHz ^{1}H NMR and 100.62 MHz ^{13}C NMR spectra were run on a Bruker AC 300 NMR spectrometer. Both ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as internal standard; Infrared spectra were recorded using a Perkin-Elmer 783 spectrometer equipped with a PE 600 data station.

III.2 Biocatalysts

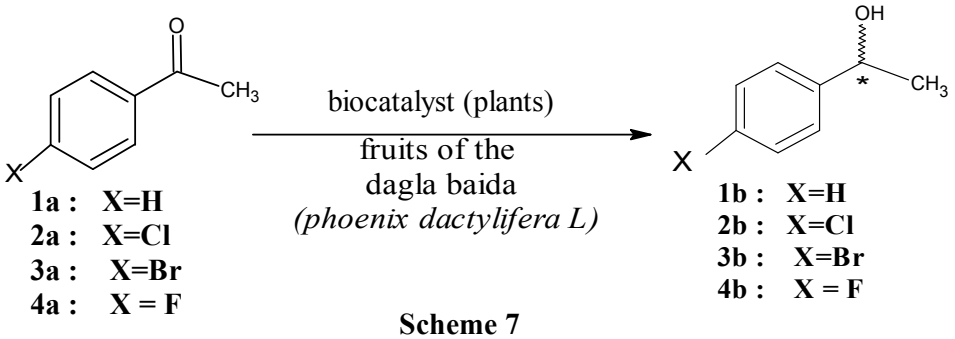
Fruits of dagla baida (Phoenix dactylifera L) was obtained from a local market. **(Scheme-4)** and washed with water, then disinfected with ethanol. was carefully cut into small thin pieces (approximately 1 cm long slice) A suspension of the dagla baida (50 g) in water (100 ml) was stirred in an Erlenmeyer fl ask at 30 ° C for 30 min. and juice of dagla baida **(Scheme-5)** obtained by mixing (50g in100ml H_2O) using an electric mixer in a slightly deionized water and stored at (25°C). Its dry powder **(Scheme-6)** was obtained after drying in the shade for about six months.

Scheme-4 pieces the dagla baida

Scheme-5: juice of dagla baida

Scheme-6 dry powder the dagla baida

A suspension of the dagla baida (Phoenix dactylifera L) (50 g in water 100 ml) was added to (0.02 mol) appropriate ketones **1a-4a** in dimethylformamide (DMF) (1 mL) **(Scheme-7),** 3% (W/V) of glucose or i-PrOH (in the case of solid ketones) as a source of hydrogen. The reaction mixture was agitated in orbital incubator shaker (150 rpm) at 30°C. The progress of the reaction was monitored by TLC. After 4 days, the plants pieces were then removed by filtration, washed with deionized water and the filtrate was extracted with petroleum ether (3x100ml). The petroleum ether fraction was dried over anhydrous ($MgSO_4$) and the solvent was evaporated to get the final product and then chemical yield and enantioselectivity were determined. Each experiment was repeated at least three times and then the average value and standard deviations were given. The products were identified by comparing their spectroscopic data with those of authentic samples[xxv-xvi]. The presence of alcoholic group in the final product was chemically confirmed by acetyl chloride test.



1a : X=H
2a : X=Cl
3a : X=Br
4a : X = F

1b : X=H
2b : X=Cl
3b : X=Br
4b : X = F

Scheme 7

III.4 Determination of optical activity of chiral products:

Optical properties of the products obtained from the prochiral were studied with the help of polarimeter Euromex Polarimeter PM. 5400 (Mitscherlich type polarimeter) using the method described in our paper reported recently [i-ii].

III.5 Identification of chiral alcohols 1b-4b by optical properties and spectroscopic data

Phenylethanol 1b:

(R)-**(1b)** was obtained in (78% yield), $[\alpha]_D^{20}$**=** +40 (*c* 5, MeOH). The absolute configuration was estimated by analogy with {Lit.[xxvii] $[\alpha]_D^{20}$=+45 (*c* 5, MeOH) for *R*-isomer}. The IR and ^1H and ^{13}C NMR spectra of **(1b)** were identical to those of authentic samples [xxv-xxvi].

^1H ($CDCl_3$, 400,15 MHz): δ (ppm): 1.48 (3H, d, CH_3CHOH-), 4.80 (1H,q,-CHOH) 3.99 (1H, br.s, OH), 7.25-7.36 (5H, m, Ar-H) **(Scheme-8) ;** ^{13}C ($CDCl_3$, 100,62 MHz): δ (ppm): 22.81(CH_3CHOH), 69.9 (-CHOH),127.1 (-CH, Ar), 127.6 (-CH, Ar), 128.9 (-CH, Ar), 146.1 (C, Ar); **(Scheme-9);** ν_{max} (KBr Disk, cm^{-1}): 3340-3060 (OH) (**Scheme-10).**

4'-Chlorophenylethanol 2b:

(R)-**(2b)** was obtained in (70% yield), $[\alpha]_D^{20}$= +22,8 (*c* 0,7 EtOH). The absolute configuration was

estimated by analogy with {Lit, [xxvii] $[\alpha]_D^{20}$= +37 (*c* 0,7, EtOH) for *R*-isomer}.The IR and ^1H and ^{13}C NMR spectra of **(1b)** were identical to those of authentic samples [xxv-xxvi].

^1H ($CDCl_3$, 400.15 MHz): δ (ppm): 1.3 (3H, d, CH_3CHOH-), 3.5 (1H, br.s, OH), 4.7 (1H, q, -CHOH), 7.0-7.3 (4H, m, Ar-H); ^{13}C ($CDCl_3$, 100.62 MHz): δ (ppm): 28.08 (CH CHOH), -1 69.54 (-CHOH), 126.93 (-CH, Ar), 128.25 (-CH, Ar), 132.94 (C, Ar), 144.44 (C, Ar); ν_{max} (KBr Disk, cm^{-1}): 3060-3340 (OH).

4'-Bromophenylethanol (3b):

(R)-**(3b)** was obtained in (60% yield), $[\alpha]_D^{20}$= +25 (*c* 1 $CHCl_3$). The absolute configuration was estimated by analogy with {Lit., [xxvii] $[\alpha]_D^{20}$= +39 (*c* 1 $CHCl_3$) for *R*-isomer}. The IR and 1H and 13C NMR spectra of (2b) were identical to those of authentic samples [xxv-xvi].

^1H ($CDCl_3$, 400,15 MHz): δ (ppm): 1.5 (3H, d, CH CHOH-), 4.7 (1H, q, -CHOH), 5.2 (1H, br.s, OH), 7.3-7.9 (4H, m, Ar-H); ^{13}C ($CDCl_3$, 100,62 MHz): δ (ppm): 28.03 (CH_3CHOH), 69.54 (-CHOH), 126.93 (-CH, Ar), 128.25 (-CH, Ar), 132.94 (C, Ar), 144.44 (C, Ar); νmax (KBr Disk, cm^{-1}): 3060-3340 (OH).

4'-Fluorophenylethanol (4b):

(R)-**(4b)** was obtained in (65% yield), $[\alpha]_D^{20}$= +30 (*c* 1 $CHCl_3$). The absolute configuration was estimated by analogy with {Lit., [xxvii] $[\alpha]_D^{20}$= +50 (*c* 1 $CHCl_3$) for *R*-isomer}.

The IR and 1H and ^{13}C NMR spectra of (2b) were identical to those of authentic samples [xxv-xxvi]. ^1H ($CDCl_3$, 400.15 MHz): δ (ppm): 1.4 (3H, d, CH_3CHOH-),3.2 (1H, br.s, OH), 4.8 (1H, q, -CHOH), 6.8-7.0 (2H, m, Ar-H), 7.1-7.3 (2H, m, Ar-H); ^{13}C ($CDCl_3$, 100,62 MHz): δ (ppm): 22.8 (CH_3CHOH), 69.9 (-CHOH), 115.7 (-CH, Ar), 126.9 (-CH, Ar), 141.7 (C, Ar), 161.8 (C, Ar); ν_{max} (KBr Disk, cm^{-1}): 3340-3060 (OH).

For all the cases, the fruits of the dagla baida *(Phoenix dactylifera L*) have given good conversion and enantioselectivity (enantiomeric excess was 60 to 89%) and the product alcohol had R-stereospecificity (**Table.1).**

Table .1: Bioreduction of acetophenone derivatives by fruits Fresh of the dagla baida *(Phoenix dactylifera L*)

Entry	Time, (Day)	Yield (%)	ee (%)	$[\alpha]_D^t$ (degrés.dm^{-1}.g^{-1}.ml)	$[\alpha]_D^t$ (of pure enantiomer)	Config.
1b	**4**	**78**	**75.5**	**+40.0**	**(*R*)+45 (c=5 in MeOH)**	***R***
2b	**4**	**70**	**62.0**	**+22.8**	**(*R*)+37 (c=0.7 in EtOH)**	***R***
3b	**4**	**60**	**64.0**	**+25.0**	**(*R*)+39 (c=1 in $CHCl_3$)**	***R***
4b	**4**	**65**	**60.0**	**+30.0**	**(*R*)+50 (c=1 in $CHCl_3$)**	***R***

III.6 Asymmetric reduction of ketones (1a-4a) catalyzed by different states of the dagla baida *(Phoenix dactylifera L)*

Due to the absence of dagla baida throughout the year, we have extended the use of dagla baida juice **(Scheme 5)** or using it dry in the form of powder **(Scheme 6)** and then we served it in asymmetric bioreduction of acetophenone derivatives. Dagla baida's juice gave a yield (43-75%) and optical purity (54-80%) **(Table 2).**

Table. 2: Bioreduction of acetophenone derivatives by different states of fruits the dagla baida *(Phoenix dactylifera L)*

Entry	State of dagla baida	Time (Day)	Yield(%)	ee(%)	$[\alpha]_D^t$ (degrés.dm^{-1}.g^{-1}.ml)	$[\alpha]_D^t$ (of pure enantiomer)	Config.
1b	Fresh	4	78	75.5	+40.0	(*R*)+45 (c=5 in MeOH)	*R*
	Dried		----	----	----		----
	Juice		50	54	+24.5		*R*
2b	Fresh	4	70	62.0	+22.8	(*R*)+37 (c=0.7 in EtOH)	*R*
	Dried		15	----	----		----
	Juice		60.5	96	+35		*R*
3b	Fresh	4	60	64.0	+25.0	(*R*)+39 (c=1 in $CHCl_3$)	*R*
	Dried		10	----	----		----
	Juice		43	82	+32		
4b	Fresh	4	65	60.0	+30.0	(*R*)+50 (c=1 in $CHCl_3$)	*R*
	Dried		----	----	----		----
	Juice		75	70	34		*R*

IV. Conclusion

In this research we have observed that the fruits of dagla baida are good biochemical catalyst, as they have the asymmetric reduction of the prochiral ketones: acetophenone **(1a),** 4-chloroacetophenone **(2a)**, 4'- bromoacetophenone **(3a)**, 4'-fluoroacetophenone **(4a)** in an easy, inexpensive and rewarding way, the yield was (40% and 78%) and optical purity (50% - 96%) especially with fresh fruits or juice, compared with the case of dry powder which gave very low yield.

V. Acknowledgments

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